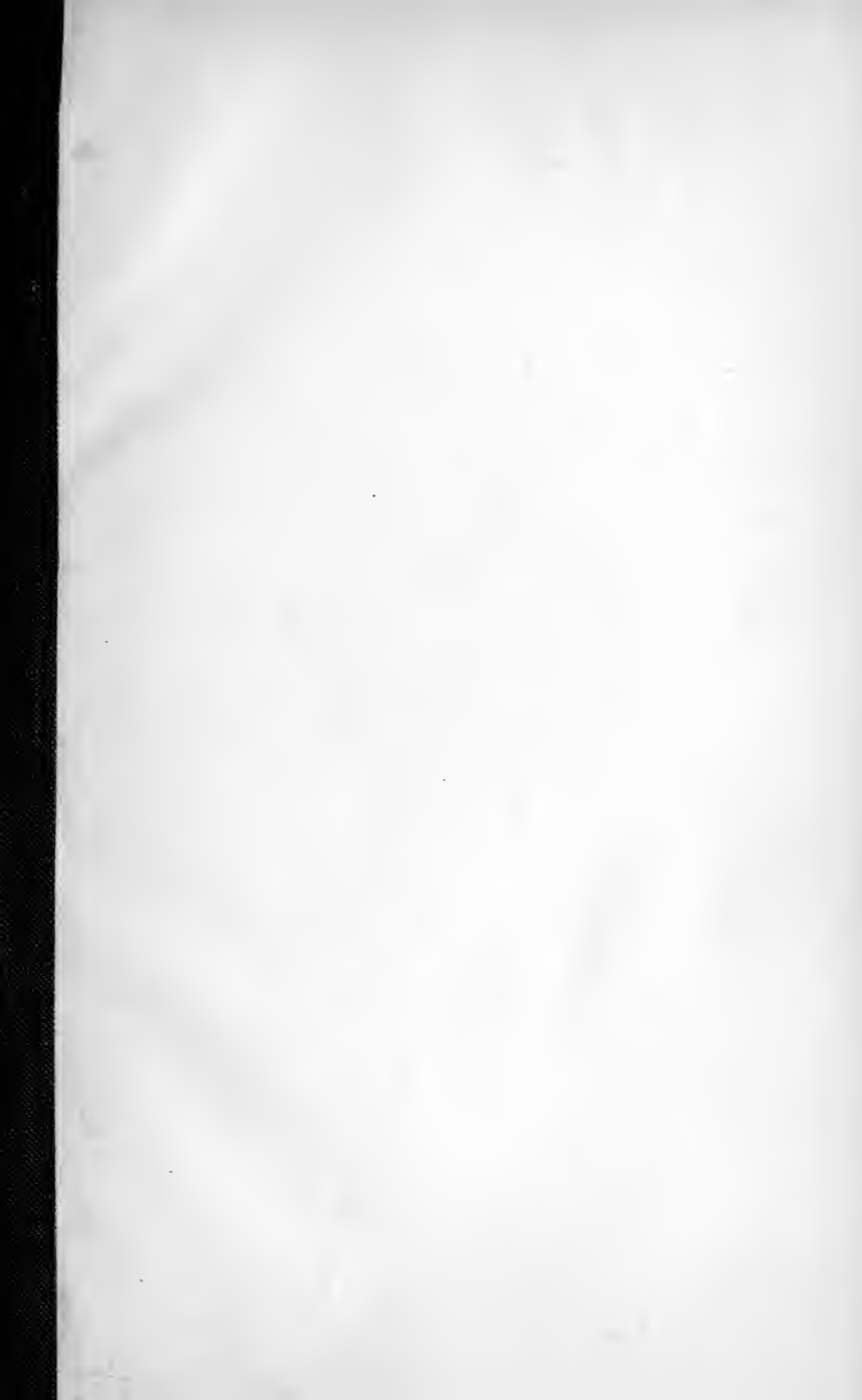


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PROCEEDINGS  
OF THE  
PATHOLOGICAL SOCIETY  
OF PHILADELPHIA.

NEW SERIES, VOLUME IV.  
OLD SERIES, VOLUME XXII.

*CONTAINING THE TRANSACTIONS OF THE SOCIETY FROM  
NOVEMBER, 1900, TO JUNE, 1901.*

EDITED BY  
DAVID RIESMAN, M.D.,  
RECORDER OF THE SOCIETY.

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PHILADELPHIA:  
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## FORMER PRESIDENTS.

SAMUEL D. GROSS, M.D., LL.D., D.C.L. Oxon., LL.D. Cantab.,  
elected 1857.

RENÉ LA ROCHE, M.D., elected 1858.

ALFRED STILLÉ, M.D., LL.D., elected 1859, '61, and '62.

EDWARD HARTSHORNE, M.D., elected 1860 and '63.

J. M. DA COSTA, M.D., LL.D., elected 1864, '65, and '66.

JOHN H. PACKARD, M.D., elected 1867 and '68.

S. WEIR MITCHELL, M.D., LL.D., elected 1869.

JOHN ASHHURST, JR., M.D., LL.D., elected 1870.

JAMES H. HUTCHINSON, M.D., elected 1871 and '72.

WILLIAM PEPPER, M.D., LL.D., elected 1873.

H. LENOX HODGE, M.D., elected 1876.

S. W. GROSS, M.D., elected 1879.

JAMES TYSON, M.D., elected 1882 and '83.

E. O. SHAKESPEARE, M.D., elected 1884.

J. C. WILSON, M.D., elected 1885 and '86.

F. P. HENRY, M.D., elected 1887 and '88.

HENRY F. FORMAD, M.D., elected 1889 and '90.

ARTHUR V. MEIGS, M.D., elected 1891 and '92.

J. H. MUSSER, M.D., elected 1893, '94, '95, and '96.

W. E. HUGHES, M.D., elected 1898.



OFFICERS AND COMMITTEES  
OF THE  
PATHOLOGICAL SOCIETY OF PHILADELPHIA.

(Elected at the annual meeting, October 11, 1900.)

**President.**

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**Vice-Presidents.**

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C. W. BURR, M.D.





## LIST OF MEMBERS.

Members marked O. M. are those originating the Society.

### ELECTED

- 1894 Abbott, A. C., 4229 Baltimore Avenue.  
1899 Adler, L. H., Jr., 1610 Arch Street.  
1898 Allen, W. L., 3100 Wharton Street.  
1889 Anders, J. M., 1603 Walnut Street.  
1900 Artelt, H., 1521 North Eighth Street.  
1891 Ashton, Thomas G., 1814 South Rittenhouse Square.  
1895 Ashton, William E., 2011 Walnut Street.
- 1897 Babcock, W. Wayne, 3302 North Broad Street.  
1898 Baggs, Albert N., Abington, Pa.  
1887 Baker, G. F., 1818 Spruce Street.  
1888 Balliet, Tilghman M., 3705 Powelton Avenue.  
1898 Bardsley, G., Episcopal Hospital.  
1885 Beates, Henry, Jr., 1504 Walnut Street.  
1900 Behrend, Moses, Philadelphia Hospital.  
1871 Bennett, Wm. H., 2105 Spruce Street.  
1887 Berens, Bernard, 2002 Chestnut Street.  
1900 Bergey, D. H., 516 North Thirty-third Street.  
1894 Beyea, H. D., 237 South Thirteenth Street.  
1892 Birney, D. B., 1810 De Lancey Place.  
1898 Blackburn, A. E., Thirty-eighth and Spring Garden Streets.  
1893 Boechroch, Max H., 987 North Eighth Street.  
1886 Bodamer, George A., 1507 Girard Avenue.  
1892 Boger, John A., 2213 North Broad Street.  
1898 Boston, L. Napoleon, 1531 South Broad Street.  
1893 Boyer, H. P., 1338 Spruce Street.  
1857 Brinton, John H., 1423 Spruce Street. (O. M.)  
1898 Brinton, Ward, 1423 Spruce Street.  
1896 Brown, H. MacV., 915 South Forty-ninth Street.  
1895 Brubaker, A. P., 105 North Thirty-fourth Street.  
1893 Bryan, J. Roberts, 4200 Chestnut Street.

## ELECTED

- 1901 Buckley, A. C., 1705 North Fifteenth Street.  
 1887 Burr, Charles W., 1327 Spruce Street.  
  
 1893 Carpenter, H. B., 1523 Locust Street.  
 1897 Carpenter, J. T., Jr., 1419 Walnut Street.  
 1900 Catanach, N. G., West Chester.  
 1887 Cattell, H. W., 3709 Spruce Street.  
 1898 Chestnut, J. E., 1757 Frankford Avenue.  
 1887 Chrystie, Walter, Bryn Mawr, Pennsylvania.  
 1899 Clarke, John G., 218 South Fifteenth Street.  
 1866 Cleemann, Richard A., 2135 Spruce Street.  
 1898 Coates, George M., 2115 Locust Street.  
 1901 Coca, A. F., 122 South Thirty-third Street.  
 1900 Codman, C. A. E., 328 South Forty-second Street.  
 1872 Cohen, J. Solis, 1824 Chestnut Street.  
 1883 Cohen, S. Solis, 1525 Walnut Street.  
 1896 Coley, Thomas Luther, 1339 Pine Street.  
 1890 Coplin, W. M. L., 1419 South Broad Street.  
 1901 Craig, F. A., Pennsylvania Hospital.  
 1899 Cruice, John M., 114 North Eighteenth Street.  
 1901 Cryer, M. H., 1420 Chestnut Street.  
 1898 Currie, Thos. R., 113 East Cumberland Street.  
 1871 Curtin, Roland G., 22 South Eighteenth Street.  
  
 1894 Da Costa, J. Chalmers, 1629 Locust Street.  
 1896 Da Costa, J. C., Jr., The Pascoe.  
 1885 Daland, Judson, 317 South Eighteenth Street.  
 1857 Darrach, James, 5923 Greene Street, Germantown. (O. M.)  
 1900 Darrah, P. W., 3439 Woodland Avenue.  
 1890 Davis, C. N., 1931 Spruce Street.  
 1882 Davis, G. G., 255 South Sixteenth Street.  
 1893 Davisson, Alexander H., 2024 Pine Street.  
 1900 Deal, J. C., 5301 Haverford Avenue.  
 1889 Deaver, H. C., 1534 North Fifteenth Street.  
 1885 Deaver, J. B., 1634 Walnut Street.  
 1882 Dercum, F. X., 1719 Walnut Street.  
 1894 Dougherty, S. W., 215 South Seventeenth Street.  
 1889 Downs, Norton, 102 West Walnut Lane, Germantown.  
 1877 Drysdale, T. M., 1305 Locust Street.  
 1866 Duer, Edward L., 1606 Locust Street.

## ELECTED

- 1876 Dulles, C. W., 4101 Walnut Street.  
1883 Dunnire, G. B., 1618 Spruce Street.  
1860 Duntun, W. R., High Street and Germantown Avenue, Germantown.  
1900 Dye, F. H., German Hospital.  
  
1900 Eaton, W. B., Jefferson Medical College.  
1896 Edsall, David L., 346 South Sixteenth Street.  
1900 Elmer, W. G., 3904 Locust Street.  
1900 Erck, T. A., 338 South Sixteenth Street.  
1891 Eshner, A. A., 224 South Sixteenth Street.  
  
1892 Fenn, William B., Denver, Col.  
1881 Fenton, T. H., 1319 Spruce Street.  
1876 Fisher, Henry M., 317 South Twelfth Street.  
1899 Flexner, S., Medical Department, University of Pennsylvania.  
1894 Fox, L. Webster, 1304 Walnut Street.  
1899 Francine, A. P., 1404 Spruce Street.  
1895 Frazier, Charles Harrison, 133 South Eighteenth Street.  
1894 French, Samuel, Plymouth, Pa.  
1889 Frese, Carl, German Hospital.  
1890 Friebis, George, 1906 Chestnut Street.  
1896 Fritz, Clarence H., 2212 South Broad Street.  
1885 Fussell, M. H., 189 Green Lane, Manayunk.  
  
1895 Garitee, C. J., 1117 Spruce Street.  
1897 Gerson, T. P., Lansdowne.  
1870 Getchell, Frank H., 1432 Spruce Street.  
1900 Gilpin, S. F., Fifty-fifth and Girard Avenue.  
1894 Girvin, John H., 3912 Walnut Street.  
1898 Gittings, J. Claxton, 4013 Chestnut Street.  
1899 Given, E. E. W., 2714 Columbia Avenue.  
1882 Godey, H. E., N. E. corner Nineteenth and Spruce Streets.  
1900 Goepf, R. M., 2121 Sansom Street.  
1890 Grayson, C. P., 251 South Sixteenth Street.  
1867 Grier, Matthew J., 1531 Spruce Street.  
1883 Griffith, J. P. C., 123 South Eighteenth Street.  
1897 Gross, Wm., 701 North Fortieth Street.  
1890 Gummey, Frank B., 5418 Greene Street, Germantown.  
1900 Gwyn, N. B., 260 South Seventeenth Street.  
1896 Haden, H. C., 346 South Fifteenth Street.

## ELECTED

- 1893 Hamill, S. M., 1822 Spruce Street.  
1893 Hand, Alfred, Jr., 1724 Pine Street.  
1885 Hare, Hobart Amory, N. W. corner Eighteenth and Spruce Streets.  
1898 Hart, Chas. D., Pennsylvania Hospital.  
1890 Hartzell, M. B., 3634 Chestnut Street.  
1900 Head, J., 1431 Walnut Street.  
1873 Hearn, W. Joseph, 1120 Walnut Street.  
1900 Hendrickson, W. F., University Dormitories.  
1870 Henry, Frederick P., 1635 Locust Street.  
1896 Henry, John N., 1635 Locust Street.  
1880 Hewson, Addinell, Jr., 1508 Pine Street.  
1901 Hickman, W. A., 4202 Parkside Avenue.  
1899 Hitchens, A. P., 1504 North Nineteenth Street.  
1899 Holloway, S. B., Fifty-fourth and Haverford Avenue.  
1894 Hughes, George M., 241 North Eighteenth Street.  
1882 Hughes, W. E., 3945 Chestnut Street.  
1901 Hunsicker, C. H., German Hospital.  
  
1890 Jarrett, Henry, Camden, N. J.  
1895 Jopson, J. H., 334 South Sixteenth Street.  
1898 Judson, Chas. F., 2010 De Lancey Street.  
1899 Jump, H. D., 4634 Chester Avenue.  
1885 Jurist, L., 916 North Broad Street.  
  
1898 Kalteyer, F. J., 1702 Pine Street.  
1895 Kelly, A. O. J., 1911 Pine Street.  
1899 Kennedy, C. P., Marcus Hook, Pa.  
1890 Ketcham, S. Rush, 1708 Green Street.  
1897 King, W. H., 412 South Fifteenth Street.  
1888 Kirby, Ellwood R., 1202 Spruce Street.  
1900 Kirk, E. C., Dental Hall, University of Pennsylvania.  
1900 Klapp, W. P., 1716 Spruce Street.  
1897 Klein, Alexander, 731 Spruce Street.  
1890 Kneass, Samuel S., University Dormitories.  
1898 Knipe, J. C., S. E. corner Fifteenth and Diamond Streets.  
1895 Krusen, Wilmer, 158 North Twentieth Street.  
1892 Kyle, D. Braden, 1517 Walnut Street.  
  
1899 Landis, H. R. M., 225 South Twentieth Street.  
1890 Laplace, Ernest, 1828 South Rittenhouse Square.

## ELECTED

- 1898 Latta, Samuel W., 3626 Baring Street.  
1894 Leach, W. W., 2118 Spruce Street.  
1869 Leaman, Henry, 828 North Broad Street.  
1888 Leidy, Joseph, 1319 Locust Street.  
1887 Leopold, Isaac, 1520 Franklin Street.  
1868 Lewis, Francis W., 2016 Spruce Street.  
1875 Lewis, Morris J., 1316 Locust Street.  
1894 Lincoln, C. W., Wayne Avenue and Coulter Street, Germantown.  
1899 Lindauer, Eugene, 1917 North Thirty-second Street.  
1886 Lloyd, James Hendrie, 3910 Walnut Street.  
1898 Lodholtz, Edward, 3103 Diamond Street.  
1894 Loeb, Ludwig, 1421 North Fifteenth Street.  
1875 Longstreth, Morris, 1416 Spruce Street.  
  
1896 McCarthy, D. J., 1342 Pine Street.  
1880 McClellan, George, 1352 Spruce Street.  
1892 McFarland, J., 421 West Price Street, Germantown.  
1894 McKee, James H., 1519 Poplar Street.  
1890 McKelway, George I., 114 South Eighteenth Street.  
1894 McLeod, George, Ardmore.  
1898 McReynolds, R. P., 3722 Walnut Street.  
1899 Masland, M. C., 2134 North Nineteenth Street.  
1892 Massey, Frank, 3604 Locust Street.  
1864 Mears, J. Ewing, 1429 Walnut Street.  
1873 Meigs, Arthur V., 1322 Walnut Street.  
1878 Mills, C. K., 1909 Chestnut Street.  
1884 Mitchell, J. K., 256 South Fifteenth Street.  
1896 Modell, D. A., 242 Fairmount Avenue.  
1900 Moore, E. K., 1715 Walnut Street.  
1857 Morehouse, George R., 2033 Walnut Street. (O. M.)  
1898 Morris, Henry, 315 South Sixteenth Street.  
1885 Morrison, William H., Holmesburg, Pennsylvania.  
1887 Morton, S. W., 113 South Twentieth Street.  
1901 Motter, M. G., 633 North Sixteenth Street.  
1869 Müller, August F., 5429 Greene Street, Germantown.  
1899 Müller, G. P., German Hospital.  
1880 Musser, J. H., 1927 Chestnut Street.  
1898 Myers, A. W., Episcopal Hospital.  
  
1879 Neff, J. S., S. W. corner Twenty-third and Spruce Streets.  
1900 Newlin, A., Pennsylvania Hospital.

## ELECTED

- 1898 Newton, R. D., 2705 Oxford Street.  
1900 Norris, G. W., 1530 Locust Street.  
1861 Norris, William F., 1530 Locust Street.
- 1894 O'Malley, James, 1104 Jackson Street.  
1900 O'Reilly C., N. E. corner Fifth-third and Haverford Avenue.  
1898 Ostheimer, A. J., Jr., Presbyterian Hospital.  
1897 Ostheimer, Maurice, 225 South Twentieth Street.
- 1885 Packard, F. A., 258 South Eighteenth Street.  
1893 Packard, F. R., 1831 Chestnut Street.  
1857 Packard, John H., Hotel Stenton. (O. M.)  
1901 Paul, F. M., German Hospital.  
1892 Pearce, F. S., 1407 Locust Street.  
1900 Pearce, R. M., University Dormitories.  
1900 Pearson, L., Veterinary Department University of Pennsylvania.  
1897 Pepper, William, 1811 Spruce Street.  
1895 Perkins, F. M., 1428 Pine Street.  
1897 Peters, L. C., 2136 Oxford Street.  
1885 Piersol, G. A., 4722 Chester Avenue.  
1893 Posey, W. C., 1831 Chestnut Street.  
1890 Potts, C. S., 1726 Chestnut Street.  
1900 Prince, D. H., Jefferson Medical College.  
1901 Purves, G. M., 750 South Tenth Street.
- 1901 Ranck, E. M., 422 North Forty-first Street.  
1885 Randall, B. A., 1604 Walnut Street.  
1898 Ravenel, M. P., University of Pennsylvania, Veterinary Dept.  
1894 Reckefus, C. H., 506 North Sixth Street.  
1885 Reed, Boardman, 1831 Chestnut Street.  
1899 Reynolds, W., 272 South South Carolina Avenue, Atlantic City.  
1894 Rhein, J. H. W., 334 South Fifteenth Street.  
1894 Riesman, David, 326 South Sixteenth Street.  
1891 Ring, G. O., S. W. corner Nineteenth and Chestnut Streets.  
1876 Roberts, John B., 1627 Walnut Street.  
1884 Robertson, W. E., 912 North Fourth Street.  
1889 Robinson, William Duffield, 2012 Mount Vernon Street.  
1899 Rodman, W. L., 1626 Spruce Street.  
1898 Rosenberger, R. C., 2330 North Thirteenth Street.  
1891 Rosenthal, E., 517 Pine Street.  
1894 Ross, George, 219 South Seventeenth Street.

## ELECTED

- 1900 Rousell, A. E., 2112 Pine Street.  
 1900 Roxby, J. B., 2222 North Nineteenth Street.  
 1896 Sailer, Joseph, 248 South Twenty-first Street.  
 1867 Santee, Eugene J., 605 North Eleventh Street.  
 1890 Sartain, Paul J., 212 West Logan Square.  
 1895 Schamberg, J. F., 1636 Walnut Street.  
 1901 Schamberg M., 1636 Walnut Street.  
 1882 de Schweinitz, G. E., 1401 Locust Street.  
 1890 Scott, J. A., 1834 Pine Street.  
 1898 Sharpless, Wm. T., West Chester, Pa.  
 1885 Shober, J. B., 1731 Pine Street.  
 1889 Shoemaker, Harvey, 109 South Twentieth Street.  
 1895 Shumway, S. A., 2007 Chestnut Street.  
 1899 Sinclair, J. F., 200 South Fortieth Street.  
 1868 Sinkler, Wharton, 1606 Walnut Street.  
 1881 Skillern, P. G., 241 South Thirteenth Street.  
 1898 Smyth, Henry Field, Germantown Hospital.  
 1894 Spellissy, Joseph M., 110 South Eighteenth Street.  
 1896 Spiller, William G., 4409 Pine Street.  
 1890 Stahl, B. F., 1502 Arch Street.  
 1894 Steele, J. D., Fortieth and Locust Streets.  
 1889 Stengel, Alfred, 1811 Spruce Street.  
 1900 Stetson, J. B. 1336 Spruce Street.  
 1889 Stevens, Arthur A., 314 South Sixteenth Street.  
 1896 Stewart, Alonzo H., 250 North Twelfth Street.  
 1886 Stewart, David D., 1429 Walnut Street.  
 1899 Stout, G. C., 1726 Chestnut Street.  
 1884 Stritmatter, I. P., 999 North Sixth Street.  
 1869 Stryker, Samuel S., 3833 Walnut Street.  
 1894 Swan, John M., 3713 Walnut Street.  
 1899 Taggart, T. D., 1825 Fairmount Avenue.  
 1900 Tally, J. E., Fifty-sixth and Lansdowne Avenue.  
 1895 Taylor, A. E., University of California, San Francisco, California.  
 1896 Taylor, J. Gurney, 6041 Drexel Road, Overbrook.  
 1897 Teller, Wm. H., 1934 Green Street.  
 1894 Thomas, W. Hersey, 1445 North Seventeenth Street.  
 1894 Thomson, Archibald G., 1426 Walnut Street.  
 1868 Thomson, William, 1426 Walnut Street.  
 1899 Tinker, M. B., 1533 Pine Street.

## ELECTED

- 1897 Tucker, Henry, 19 South Twenty-first Street.  
1898 Twaddell, Thomas, 4203 Chester Avenue.  
1863 Tyson, James, 1506 Spruce Street.  
1890 Tyson, T. Mellor, 1506 Spruce Street.  
  
1900 Uhle, A. A., German Hospital.  
  
1895 Vandervoort, C. A., 3250 North Fifteenth Street.  
1887 Vansant, Eugene L., 1929 Chestnut Street.  
  
1898 Wadsworth, W. S., 227 South Thirty-sixth Street.  
1891 Wallace, James, 350 South Sixteenth Street.  
1899 Walsh, J. P., Forty-eighth and Chester Avenue.  
1890 Warder, C. B., 1401 North Sixteenth Street.  
1874 Warder, W. H., 1212 North Broad Street.  
1895 Wendell, W. G., 4126 Chester Avenue.  
1887 Westcott, T. S., 1833 Spruce Street.  
1885 Wharton, H. R., 1725 Spruce Street.  
1897 White, Courtland Y., 334 South Sixteenth Street.  
1873 White, J. William, 1810 South Rittenhouse Square.  
1893 Whiting, A. D., 1523 Spruce Street.  
1868 Willard, De Forest, 1818 Chestnut Street.  
1898 Willson, R. N., 350 South Fifteenth Street.  
1869 Wilson, James C., 1437 Walnut Street.  
1891 Wilson, Samuel M., 1517 Arch Street.  
1891 Wilson, W. R., 112 South Twentieth Street.  
1895 Witmer, A. F., 1328 Pine Street.  
1898 Woldert, E. A., 1709 North Sixteenth Street.  
1890 Wolff, L., 333 South Twelfth Street.  
1890 Wood, A. C., 128 South Seventeenth Street.  
1898 Wood, George B., 129 South Eighteenth Street.  
1865 Woods, D. Flavel, 1501 Spruce Street.  
1897 Woodward, E. B., 4222 Chestnut Street.  
1898 Woodward, G., Chestnut Hill.  
1899 Worden, C. B., 4208 Walnut Street.  
  
1897 Yarrow, Thomas J., Jr., 1739 North Sixteenth Street.  
  
1895 Zimmerman, Mason W., 1522 Locust Street.



## NON-RESIDENT MEMBERS.

Baines, A. S., Jr., 4484 Finney Avenue, St. Louis, Mo.  
Ball, M. V., Warren, Pa.  
Breinig, P. B., Bethlehem, Pa.  
Brooke, B., Radnor, Pa.  
Carter, W. S., Galveston, Texas.  
Cerna, D., Galveston, Texas.  
Dock, George, Ann Arbor, Mich.  
Edwards, W. A., San Diego, Cal.  
Egbert, Joseph P., Wayne, Delaware County, Pa.  
Eskridge, J. T., Denver, Col.  
Fox, J. M., Torresdale, Pa.  
Gaylord, H. R., Buffalo, N. Y.  
Hamaker, W. D., Meadville, Pa.  
Hamann, C. A., 517 Euclid Avenue, Cleveland, Ohio.  
Harris, H. F., Atlanta, Georgia.  
Harrison, W. H., Harrisburg, Pa.  
Hatch, John L., 2010 Fifth Avenue, New York City.  
Hileman, J. B., Altoona, Pa.  
Hiller, H. H.  
Holder, C. A., Colorado Springs, Col.  
Howard, F. H., Williamstown, Massachusetts.  
Hunt, J. R., New York.  
Izard, W., Camden, New Jersey.  
Jamar, John H., Elkton, Md.  
Johnston, J. A., National Soldiers' Home, Virginia.  
Lincoln, W. R., Cleveland, O.  
Muhlenberg, Frank, Reading, Pa.  
Nancrede, C. B., Ann Arbor, Mich.  
Osler, William, Johns Hopkins Hospital, Baltimore, Md.  
Pease, H. D., Buffalo, N. Y.  
Pfouts, G. B., Morris Plains, N. J.  
Powell, W. M., Atlantic City, N. J.  
Rahter, C. A., Harrisburg, Pa.  
Rivas, Damoso, Lille, France.  
Schreiner, E. R., U. S. A.  
Slifer, Henry F., North Wales, Pa.

Smith, Allen J., Galveston, Texas.  
 Stadelman, E., Durango, Mexico.  
 Stiles, G. A., Conshohocken, Pa.  
 Stubbs, R. P., Wilmington, Delaware.  
 Taylor, L. H., Wilkesbarre, Pa.  
 Toulmin, H., Haverford, Pa.  
 Wells, G. M., Wayne, Delaware County, Pa.  
 Wetherill, R. B., Lafayette, Ind.  
 White, Frank, Elwyn.  
 Williams, H. L., Minneapolis, Minnesota.  
 Wilmarth, A. W., State Home for the Feeble Minded, Chippewa Falls,  
 Wisconsin.  
 Ziegler, J. L., Mt. Joy, Pennsylvania.

## CORRESPONDING MEMBERS.

### ELECTED

1866 Bumstead, Freeman J. Deceased.  
 1859 Clark, Alonzo, New York. Deceased.  
 1898 Cornil, V., Faculté de Médecine, Paris, France.  
 1859 Dalton, J. C., New York. Deceased.  
 1885 Dent, Clinton T., Assistant Surgeon and Lecturer on Practical  
 Surgery at St. George's Hospital, Surgeon to Belgrave Hos-  
 pital for Children, London, England.  
 1860 Ellis, Calvin. Deceased.  
 1888 Fedeli, Gregorio, Rome, Italy.  
 1858 Flint, Austin, Sr. Deceased.  
 1890 Gibbes, Heneage, Ann Arbor, Michigan.  
 1858 Hammond, William A., New York. Deceased.  
 1860 Isaacs, Charles E., Brooklyn. Deceased.  
 1878 Jackson, J. B. S., Boston. Deceased.  
 1886 Pye-Smith, P. H., Physician and Lecturer on Medicine at Guy's  
 Hospital, London, England.  
 1860 Reeves, James E., Wheeling, West Virginia. Deceased.  
 1861 Rokitsansky, Carl. Deceased.  
 1898 Virchow, Rudolf, Berlin, Germany.  
 1860 Watson, John, New York. Deceased.  
 1898 Welch, William H., Professor of Pathology, Johns Hopkins  
 University, Baltimore, Maryland.  
 1859 Worthington, Wilmer, West Chester, Pennsylvania. Deceased.

# Proceedings

of the

## Pathological Society of Philadelphia.

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NOVEMBER 1, 1900.

NEW SERIES, VOL. IV. NO. 1.

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### TABLE OF CONTENTS.

Dr. Edward O. Shakespeare.—PACKARD, Address of the President.—FLEXNER, Nature and Distribution of the New Tissue in Cirrhosis of the Liver. (Preliminary Communication.)—NOGUCHI, The Effect of Cold Upon the Vitality of the Bacilli of Bubonic Plague.—ESHNER, Cerebral Hemorrhage.

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### DR. EDWARD O. SHAKESPEARE.

At a meeting of the Pathological Society held on October 25, 1900, the undersigned committee presented the following minute which was adopted and ordered printed in the PROCEEDINGS of the Society :

Edward O. Shakespeare was born May 19, 1846, and died June 1, 1900. Gifted by nature with talents of the highest order, he so used them as to leave an indelible impression upon medical science. His interests were wide, and embraced ophthalmology, histology, pathology, bacteriology, and sanitary science. In addition, he was a linguist, a skilful etcher on stone, and a master of the art of photography, particularly of that difficult branch, microphotography.

As an ophthalmologist, he was not only a conscientious and successful practitioner, particularly in hospitals, but also a scientist and an inventor, having devised, among other things, an ophthalmoscope for use in the study of the eyes of human beings and animals.

The thorough knowledge of histology which he possessed is shown in the splendid chapter on that subject contributed by him to Harrison Allen's *Anatomy*. His researches in pathology are

largely contained in the TRANSACTIONS of this Society, of which he was President in 1884 and 1885, and in various articles contributed to medical journals; in the translation of Cornil and Ranvier's *Manual of Pathological Histology*, and in the *Toner Lecture* of 1879, in which he dealt with the nature of the reparatory changes in arteries after ligation, acupuncture, and torsion.

In later years his chief interest was centered in bacteriology, and it is his work in this science that will forever constitute the pedestal of his fame. His able defence of the specificity of the tubercle bacillus against the powerful assaults of Dr. Formad and others was based upon a thorough knowledge of the subject, and attracted the widest attention.

As a sanitarian he will always be remembered for his masterly study of the typhoid fever epidemic at Plymouth, Pennsylvania, by which he was able to demonstrate beyond cavil the water-borne character of the disease, and for his exhaustive researches on cholera made under the auspices of the United States Government in 1885 and 1886. His official report, in the preparation of which he spent four years, and for which he received no pecuniary remuneration, comprises 899 quarto pages and 105 illustrations, nearly all original. It is a monumental work—the most comprehensive one ever written upon the subject—and will remain an enduring exemplar for future investigators in the domain of epidemiology.

D. RIESMAN,  
J. H. MUSSER,  
W. E. HUGHES,  
Committee.

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Address of the President.

FREDERICK A. PACKARD, M.D.

According to custom and to a provision of the by-laws, upon the last meeting of his term of office the President of the Pathological Society delivers an annual address. This is apparently intended to give a summary of the work done during the year, and to pat ourselves upon the back or make anew good resolutions in accord-

ance with the results of the year's work. Glancing at the year as a whole, it will be found that it has been quite a successful one. We have held nineteen meetings, with an average attendance of thirty-two, showing, therefore, no falling off in the interest of the members. Most of these were the regular stated monthly meetings, with volunteer reading of papers and exhibition of specimens. These numbered eighty, or an average of about five papers or specimens at each meeting. The two exceptions were our annual conversational meeting, which was held in April, and at which an address was delivered by Dr. Theobald Smith upon "Comparative Pathology; Its Relation to Biology and Medicine," and another meeting out of the ordinary, which was held in January, and was occupied by a Symposium on Typhoid Fever. Dr. Theobald Smith's paper was a scholarly address upon a subject which is attaining more and more wide and deserved attention. The Symposium on Typhoid Fever was one calculated to interest alike the hygienist, the clinical pathologist, and the practising physician. The meeting was sufficiently successful both in the character of the papers read, the scope of the subject that was covered, and the attendance upon the meeting to make it seem advisable that the Business Committee should arrange for similar meetings in the future.

Before speaking of the actual papers read at our ordinary meetings, I would like to refer to what has been mentioned in the annual address of my predecessor—the publication of our TRANSACTIONS in the form of monthly fasciculi. The method has proven most satisfactory, as is evidenced by the expressions of opinion by members of the Society, by the frequency with which abstracts of our proceedings are found in the various foreign journals, and by the improvement in the character of the papers that follow upon the knowledge that they will appear without delay and before the subject-matter of the paper has had time to grow stale. By the present method of publication we get less of an idea as to the amount of work done in particular lines, owing to the fact that with the separate fasciculi we lose the grouping in regard to subjects which gave at a glance the amount of work done upon particular lines during the period covered by the bound volume of the TRANSACTIONS as it appeared formerly. It has seemed to me,

therefore, that this want might be somewhat supplied by a *résumé* of some of the papers in the Presidential Address. The only difficulty in doing this has been that it seems somewhat invidious to designate particular papers. A *résumé* of all the contributions would, of course, be out of place, yet I think it is a pardonable matter for us to see to what extent the work brought before us is contributing to the advancement of knowledge in the various important subjects in regard to pathology that are at present receiving most attention.

On looking over old volumes of the TRANSACTIONS OF THE PATHOLOGICAL SOCIETY there are found to be a fair number of exhibitions of specimens illustrating comparative pathology. To the Business Committee this has always seemed to be a branch deserving of our encouragement in arranging for the meetings for the year, and it is a notable fact that when specimens have been presented the interest of the members in coming forward to examine them has always been very evident. During this year there have not been presented as many specimens of this kind as we might hope to have. Those that have been shown have been the organs of a lioness which died of suffocation from impaction of meat in the larynx; a series of frogs presenting interesting and remarkable congenital anomalies, and a noteworthy specimen of aneurysm occurring in a chicken. It is to be hoped that during the next year more specimens of this character will be exhibited, particularly from the fact that comparative pathology is occupying a more and more prominent place, especially since its bearing upon human pathology has been particularly pointed out by such workers as Bland Sutton and others who have shown the relationship between disease in the human being and what were at one time considered as matters of interest only to students of natural history. We have been fortunate in having during the past year several results of experimental studies presented to us; among these I would particularly mention the paper of Flexner upon experimental pancreatitis, which throws additional light upon this but little understood pathologic condition.

The relation of tuberculosis to various species of animals is a subject that is of extreme importance, not only because of its general

interest, but because of its bearing upon questions of hygiene. The use of goats' milk for the nourishment of children has been urged, partly because this animal is supposed to be but little prone to tuberculosis. Ravenel and White have shown us specimens of the experimental production of tuberculosis produced by the inoculation of pure cultures of tubercle bacilli from a cow through the chest-wall into the lung of a goat. The importance of this observation can be readily seen when we bear in mind that autopsies upon goats are seldom conducted with such care as to enable us to get at the exact danger involved in using the milk of this animal in the nourishment of children.

Another point of interest to the hygienist is covered by a paper by Ravenel upon "The Transmission of Syphilis to Calves." This is particularly timely now, because of the idiotic attacks of the antivaccinationists upon the propriety of protection from small-pox. Ravenel's failure in two cases to produce the disease by the inoculation of the syphilitic virus is a valuable contribution to contradict the absurd claims of a set of fanatics, that "loathsome diseases," by which, in the majority of cases, they mean syphilis, can be inoculated with the material of the vaccine.

The paucity of articles dealing with bacteriology that have been read during the past year is doubtless due to the absence of proper means of demonstration at our meetings. Could we have a proper projection-apparatus by which slides could be thrown upon a screen, doubtless many more papers dealing with bacteriology would be presented. Among other papers which incidentally have dealt with the subject of bacteriology and allied subjects are those of Walsh, describing a sarcina pathogenic for guinea-pigs, which was obtained from the spleen of a child; a paper by Pearson and Ravenel upon pneumonumycosis due to the *aspergillus fumigatus*, and a paper by McFarland upon the bacillus of plague, a subject that is one of very active interest at the present time. Among the infections that have been dealt with in the papers that have been read during the year, or of which specimens have been shown, are typhoid fever, typhus fever, cerebrospinal meningitis, anthrax, bubonic plague, rabies, and tuberculosis. The preliminary report upon the rapid diagnosis of rabies, made by Ravenel and McCarthy at the meeting of June 14th, is of value in

confirming the work of Nelis and Van Gehuchten as to the changes in the intervertebral ganglia of the spinal cord. The importance of some means of rapid and certain determination of the existence of true hydrophobia makes such work as that covered by the article of much value, which will probably be greater in the future when our means of combating the disease are more established, while by an exact method of making a pathologic diagnosis the claims that are constantly being advanced that there is no such disease among the human species may be either confirmed or refuted.

At a recent meeting tuberculosis in cats was the subject of a paper, and we have had presented at one of our meetings specimens of cutaneous tuberculosis apparently proven to have been due to inoculation by the bovine bacillus, a question that is of much interest at the present time, when doubt is being thrown upon the identity of the bacillus producing tuberculosis in man and in the lower animals. Somewhat allied to this last paper was the one upon tuberculosis of the skin of the hand, reported by Schamberg.

The subject of internal secretions, and especially the existence and nature of an internal secretion from the pancreas and its connection with diabetes mellitus, makes this organ one of the most important subjects of study at the present time. We have had several interesting specimens of pancreatic disease presented at our meetings, beside the specimen of experimental inflammation of that gland that accompanied the paper of Flexner, mentioned above. The physiology and pathology of the suprarenal capsules are still sufficiently in the dark to make these organs extremely interesting objects of study, not only from the stand-point of physiology and pathology, but also because of the use of suprarenal extract as a drug. Specimens from two cases of Addison's disease have been shown, one from a negro; we have also had before us an example of hemorrhagic infiltration of the suprarenals and kidneys from an infant.

Among other papers dealing with the central nervous system, of which we have had quite a large number, I would mention as particularly valuable the "Report of a Case of Polioencephalomyelitis Presenting the Appearance of Landry's Disease," following a dissecting wound; specimens from a case of hematomyelia; exhibition of the malarial parasites in the capillaries of the central



nervous system, and a specimen of a tumor of the pituitary body found in a case of *adiposis dolorosa*.

Of illustrations of diseases of the circulatory system we have had a large and interesting number presented. I would especially call attention to the paper by Meigs upon "Endophlebitis," which is an elaborate study upon a subject that has received but little attention.

Owing to the activity of our surgical friends the appendix is more frequently seen than if we had to depend upon autopsies for obtaining a supply. Useless as the organ is in our economies, it has been the subject of extremely interesting papers during the past year. Of these I would particularly mention a paper by Kelly upon tumors of the vermiform appendix, and an elaborate article by Jopson upon hernia of this portion of the intestine.

When we bear in mind that in addition to those papers to which I have briefly alluded we have had the usual run of specimens occurring in the daily work of the members, it will be seen that we have had a very active year and one of which we may well be proud.

There are two ways in which it seems to me we might improve the field of our work. One of these has already been alluded to—I refer to the use of a projection-apparatus and screen. This would enable us to save a great deal of time which is now lost by the members coming forward to examine specimens under the microscopes. While this is time well spent, it is evident that something must be done to facilitate matters, especially as there is a constantly growing and very gratifying increase in the number of histologic specimens exhibited, either independently or with the gross lesions.

Another feature upon which we might lay more stress is the exhibition of card specimens. Between the autopsies at the various hospitals and those made in private practice a very large number of specimens are obtained each week in this city. The rarer specimens are at times shown in the fresh condition; many, however, of those of greatest interest are placed in preservative fluid with the idea of delaying their exhibition until the subject has been thoroughly worked up. Doubtless each of us has, with the best intentions in the world, set aside many of these specimens,

and has not been able, owing to the press of other work, to present them in a completely worked-up form. Even though the specimens are ultimately shown they cannot be exhibited to as great an advantage after the use of preservatives as shortly after their removal. It is a pity that some provision is not made by which an exhibition of such specimens preliminary to the final report might be made. Such an exhibition would not interfere with the ultimate more careful study of the case, and would certainly be to our advantage. Many specimens are removed which are too commonplace to make us think of writing out a detailed report of the case, or of announcing the exhibition of the specimen, yet we can never see too much of the ordinary lesions encountered in the routine making of autopsies. Some such plan as the Business Committee attempted to adopt two years ago, by which specimens could be arranged in a manner to permit of their ready inspection, with an accompanying card giving a brief description of the specimen, and possibly some points in the clinical history, would certainly be an advantage. If one of us has a well-marked instance of some such lesion as mitral stenosis or cirrhosis of the liver, he is apt to neglect showing it at the Society meetings because he feels that there is nothing particular to say about it that would warrant its announcement on the program. From the interest manifested by the members of the Society in coming forward to look at specimens of lesions which they have frequently seen before, I do not doubt that a table covered with card specimens would attract a considerable amount of attention and add to the interest of the meetings. These could be examined either before the meeting, after the meeting, or during the times when others are crowding around specimens illustrating a paper which has just been presented. I am sure that with the plan once carried out for a few meetings, not only would the number of card specimens steadily increase, but the members would feel a new interest in coming to the meetings.

While our life during the past year has been a successful one, it has in other ways been an unfortunate year for the Society. During the past twelve months we have lost by death four of our former Presidents, Alfred Stillé, J. M. Da Costa, John Ashhurst, Jr., and E. O. Shakespeare. Proper action upon their death will be taken by

committees appointed by direction of the Society, but I cannot refrain here from merely alluding to the loss of four men who, though for some time taking no active part in the Society's transactions, have in the past largely contributed to its success and been an honor to its membership-roll. Another member of the Society whose death has occurred within the last year is Thomas S. Kirkbride, Jr. With his intense enthusiasm, his thorough training, and the advantages which he had taken of his opportunities, we may feel sure that had he lived he would have taken a leading part in our proceedings. Even as it is, I cannot but feel that his interest in his profession has had an influence for good upon those of us who were thrown with him, and that the work which he started with so much zeal in the laboratory of which he was the head will be productive of good and lasting results.

In closing, I would merely express the pleasure that I have felt in presiding over the meetings of the Pathological Society and my appreciation of the honor that has been conferred upon me in allowing me the privilege of serving in the same position that has in the past been adorned by so many illustrious names of Philadelphia physicians.

*October 11, 1900.*

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### Nature and Distribution of the New Tissue in Cirrhosis of the Liver. (Preliminary Communication.)

SIMON FLEXNER, M.D

Much has been written upon the histologic changes of the liver in cirrhosis. The main attention, however, has been paid to the problem concerning whether the interstitial elements or the liver cells are primarily affected. Hitherto it has been deemed sufficient to speak of the increased interstitial tissue simply as connective tissue. The introduction of specific stains, especially in the last two years, for demonstrating elastic tissue has made it possible to determine what part of this so-called connective tissue is of the nature of the former tissue. The application, moreover, of certain dissociating technic methods previously employed in purely histologic studies to the elucidation of the same problem has also led

to the further differentiation of the several tissues concerned in the production of the "fibrosis" of cirrhosis.

That white fibrous tissue is contained in the human liver, especially in the interlobular spaces, has, of course, been known for many years, but that reticulum is also a regular constituent of this organ and permeates the lobules we have come to know since the studies of digestion by Mall (*Johns Hopkins Hospital Reports*, vol. i. p. 171). We may, however, say that, so far as the technic methods are capable of indicating at this time, there is evidence of the occurrence of the three several kinds of connective tissue—white fibrous tissue, elastic tissue, and reticulum—within the liver, but that the distribution of the tissues varies. The ordinary white fibrous tissue is found with the bloodvessels, being therefore chiefly marked and in the largest quantity in the interlobular spaces. Reticulum, on the other hand, occurs especially within the lobule; the fibrils are fine, and not usually demonstrable in stained preparations. The elastica in the normal organ is present chiefly within and about the bloodvessels. It occurs also, as will be seen, in Glisson's and the surface capsules and in the bile-ducts.

The quantity of elastic tissue varies with the age of the individual. In children it is present in less amount than in middle age, and in the latter it is less abundant than in old age. The chief elastic tissue is contained in the bloodvessels and in Glisson's capsule, but it is found in the hepatic vessels and their branches, with the exception of the central veins, where it is usually absent, or, if present at all, it occurs in very small amount.

The hepatic arteries and portal veins contain a well-developed elastic membrane in the adventitial coats, the fibers composing the network being quite uniform in size. The muscular coats, especially of the arteries, are relatively free from fibers. The bile-ducts, on the other hand, are distinguished from the bloodvessels, inasmuch as the layer of elastic tissue in the wall next the epithelium consists of a very delicate fibrillar network, while in the external layer, which corresponds with the adventitia of the bloodvessels, a thicker network occurs. A cross section through the interlobular vessels shows that the elastica of the external layer of the portal vein, hepatic artery, and bile-ducts unite into a network which surrounds, as a general capsule, the interlobular

vascular system. Neither the surface nor the interlobular capsule sends elastic fibers into the interior of the lobules. The stroma of the lobules in normal organs consists solely of collagenous tissue.

Our knowledge of the distribution of the elastic tissue in the liver, both in health and in disease, we owe to the studies of Melnikow-Raswedenkow (*Ziegler's Beiträge*, 1899, xxvi. p. 526). The studies made by him upon such pathologic conditions as atrophy, chronic congestion, and cirrhosis have led him to conclude that in chronic morbid hepatic processes associated with an overgrowth of connective tissue, the overgrowth is chiefly composed of elastic tissue. In simple atrophy of the organ the elastic tissue develops in the periphery where the atrophy usually begins.

Cirrhosis—atrophic, mixed, and hypertrophic—gives rise to various grades of the new formation of elastic tissue, depending upon the degree of the atrophy, the duration of the process, and probably its nature. More elastic tissue is found in the atrophic cirrhosis than in the mixed, and more in this than in the hypertrophic. The elastica uses the interlobular vessels, especially arteries, portal veins, and bile-ducts for its origination, but sometimes the hepatic veins are employed. The elastic elements are found especially in Glisson's capsule, but sometimes they penetrate into the acini between the rows of liver cells.

The studies which shall be reported briefly in this paper were carried out in the Pathological Laboratory of the University of Pennsylvania by Drs. Hatfield and Goepp. They had for their thesis the determination of the nature and distribution of the newly-formed tissue in cirrhosis. Account was taken not only of the normal and pathologic distribution of the elastic tissue, but equally of the white fibrous tissue and reticulum. Commonly the three tissues were followed in the same organ, and a comparison of the results of the use of special technic methods as applied to them was made.

**METHODS OF STUDY.** *Elastica.* Two methods are now open to use for the demonstration of this tissue, both being in the nature of specific stains; the first is that of Unna, in which orcein is employed, and the other that of Weigert, which employs a resorcin and fuchsin combination. The early experiments with Unna's method were very unsatisfactory, because it was found that the

staining was irregular and inconstant. On the other hand, Weigert's method gave from the beginning a constant result; it was therefore employed to the exclusion of the former method.

In the study of the amount and distribution of the elastic tissue, recourse was had to the method of digestion, for the purpose of controlling the results obtained with Weigert's stain. Inasmuch as elastica quickly disappears under the influence of pancreatic digestion that element could easily be eliminated, while the remaining connective tissues were retained in the sections, thus affording a check upon the perfection of the selective stain.

*Reticulum.* For the purpose of demonstrating the tissue within the lobules of the liver, the digestive method, as first introduced by Mall, as well as the modification of Spalteholz were utilized. By these methods both fresh and preserved tissues in sections are digested in an alkaline solution, by means of pancreatin, when the parenchymatous cells and the elastic tissue are completely removed. There remains behind a framework consisting of white fibrous tissue and reticulum. Mall has shown us what the normal intralobular distribution of the reticular tissue is. Comparisons are easily made between the normal and the pathologic condition as found in cirrhosis.

*White Fibrous Tissue.* In the study of the white fibrous tissue of the liver, stained sections, both before and after digestion, were employed. Beside the ordinary stains for that tissue, and the reticulum stains which also color it, the recent specific stain of Mallory was employed. The last staining method was found especially useful in demonstrating the fine fibrils of white fibrous tissue contained within the liver lobules; but inasmuch as this stain also colors the reticulum, its use is somewhat more limited than could be wished; on the other hand, it apparently leaves the elastic fibers unaffected. Attempts were made to eliminate the white fibrous tissue by digestion in caustic alkaline solutions, but with very imperfect success.

*Elastica.* For the purpose of studying the pathologic distribution of this tissue well-marked examples of cirrhosis, both atrophic and hypertrophic, as well as specimens of the liver which macroscopically appeared normal, but in which a slight proliferation of cells in interlobular tissue had taken place, were employed.

**ATROPHIC CIRRHOSIS.** In a case of nodular cellular new growth small accumulations of lymphoid cells occur in the interlobular tissue. These foci of cells are usually quite small and do not penetrate into the lobules. There is a very slight, indeed, almost unappreciable, growth of ordinary fibrillated connective tissue within these nodules. On the other hand, finer and coarser fibrils of elastic tissue appear among the cells. The larger the periportal space the coarser the fibrils that occur in the cellular nodules. In another specimen of localized interlobular increase in the connective tissue, in which, however, the new tissue is very poor in cells, there is a very marked increase in elastic tissue. This tissue forms a quite uniformly meshed network, surrounding the vessels and extending throughout the connective-tissue growth. There is in this case almost no attempt to invade the intralobular tissue. In marked examples of perilobular cirrhosis specimens stained for elastic tissue, and observed by the naked eye, present an insular appearance. The islands are pale in appearance, vary in size from a fraction of a lobule to several lobules, and are separated by dark lines of elastic tissue. Microscopic examinations show that these dark bands correspond partially with the hypertrophied strands of Glisson's capsule, some, however, proceeding from the surface capsule and extending into the liver substance.

The indentations of the surface correspond with the depressed masses of fibers. There is a continuation of the elastic tissue in the capsule with the invading processes within the liver. The fibers in the capsule are arranged in the form of a crenated and closely woven network. A similar structure is apparent in the continuation within the liver. Newly-formed and dilated blood-vessels, the walls of which are composed of such fibrillated tissue, are associated with the new growth. In some places the new tissue within the liver substance consists of very closely anastomosing bands, in the midst of which are the remnants of liver lobules. Not all of the dense tissue stains sharply, but the sharply stained fibers have the same meshed and crenated appearance as is seen about the capsule, and they proceed from the walls of bloodvessels and bile-ducts. In the specimen being described there are a fair number of so-called newly-formed bile-ducts; these, it should be emphasized, differ from the normal bile-ducts

in that they present an imperfect development of elastic tissue about them, or they may be entirely deficient of such fibers. It is evident from the specimens that much of the new growth of interlobular tissue is not, properly speaking, elastic tissue. The new formation of elastic tissue in this form of cirrhosis does not remain limited to the periportal tissues. Just as in this condition the ordinary connective tissue invades the lobules, so may the elastic tissue appear in that situation. The degree of invasion is variable, but in such specimens as I have examined it is not common to find much new elastic tissue within the lobules unless these structures have been more or less completely destroyed by the new growth of tissue. The elastic tissue penetrates along the line of liver cells, usually in the form of fine bands or strands. In an instance of perilobular cirrhosis in which there was much cellular infiltration and penetration of the small cells, in the form of nodules into the lobules, fine, wavy, and anastomosing fibrils of the elastic tissue were present within the intralobular cellular accumulations.

**HYPERTROPHIC CIRRHOSIS.** The changes in this condition, which will be described, are based upon a small number of cases in which the livers were markedly enlarged and the surface smooth or very slightly indented. Weigert's stain indicates that much of this tissue is composed of elastica, which is present in the form of bands, composed of branching, anastomosing fibers, many of them either starting from or reaching the surface capsule. Where indentations of the surface are present they correspond with these bands. The sections are cut up into irregular islands of pale color by the bands of blue-stained fibrils which proceed from the interlobular tissue. In addition to these grosser bands, fine wavy lines extend into the lobules, subdividing these units into much smaller units, composed of a few liver cells or even single cells. The fibrils last described often suggest continuity with the reticulum and the capillary walls that exist between the rows of liver cells. This intralobular growth may be extremely fine and very diffuse, so that the impression is obtained that a large part of the increase in size of the liver is brought about by this intercalation. The very minute fibers come out with such distinctness as to suggest that they might have been drawn with a pen.



*Reticulum.* For the study of the changes in the reticulum, several different specimens of atrophic and two specimens of hypertrophic cirrhosis were employed. The fresh tissue was studied by Mall's method, and the hardened tissue by the method of Spalteholz.

**ATROPHIC CIRRHOSIS.** In an extreme grade of this form of cirrhosis digested specimens show a very large amount of new tissue in the periphery of the lobules and an intralobular invasion of coarse fibrils derived immediately from the extralobular growth. Whenever the lobules have been greatly encroached upon the reticulum is correspondingly reduced in volume; but what remains has not necessarily undergone any change in arrangement and in the size of the individual fibrils. On the other hand, the ingrowth of white fibrous tissue would appear to take place in such a way as to utilize the arrangement afforded by the reticular fibers. At first sight it might be supposed that the coarse fibers just mentioned are a modified reticulum, but serial sections show that they are connected with the peripheral new growth of tissue. The great difficulty of separating by chemical means reticulum and white fibrous tissue makes it impossible to say whether, after all, some of the coarser fibers within the lobules in this case may not be reticulum. What is, however, very important, and should be emphasized, is that after digestion and the elimination of all of the elastic fibers there still remains behind a large amount, indeed, apparently as large a volume as before, of collagenous fibrils.

In other specimens in which the perilobular growth is less marked than in the previous instance, interesting changes were made out in the reticulum. In these specimens there is little or no invasion from without. The architecture of the reticulum is preserved in its normal arrangement, but the individual reticular fibers are hypertrophied, the greatest degree of thickening occurring in the periphery near the thickened interlobular tissue. While equally hypertrophied fibers are also found well removed from the peripheries in the centers of the lobules, yet at the same time I prefer to speak guardedly with reference to their ultimate nature. I think it possible that the fibers have proceeded from the interlobular tissue, in which case they are not, *a priori*, to be regarded

as reticulum. On the other hand, if these fibers are of the nature of white fibrous tissue, they represent an intralobular invasion from the periphery, which ordinary methods would not expose. It should be mentioned here that the study of the finer intralobular growth of the connective tissue is likely to be much facilitated by the new staining method for fibrous tissue recently introduced by Mallory (*Journal of Experimental Medicine*, 1900, vol. v., No. 1).

**HYPERTROPHIC CIRRHOSIS.** The limited number of specimens (2) which have been open to study will not permit of any far-reaching conclusions being drawn. The main alterations, as shown by these cases, consist of a much more moderate new growth of tissue in the periphery of the lobules and a finer invasion of the lobules than in the previous class of cases. The difference between the original reticular fibers and the newer fibers is easily made out by the relative coarseness of the fibers and by their arrangement. While in a general way they follow the arrangement of the reticulum, they are in places so increased as to obliterate the original architecture, and, in addition, they come together in what might be termed centers, from which the fibers radiate in all directions. These stellate centers form a good index of the degree of lobular invasion.

*White Fibrous Tissue.* This tissue has been considered in two previous sections. All attempts to eliminate it from the preparations by means of caustic alkalies were more or less unsuccessful. By exclusion of the elastic element, on the one hand, and the consideration of the reticulum on the other, the conclusion was reached that white fibrous tissue is a constant and abundant constituent of all forms of marked cirrhosis, that in certain very cellular examples it is present in small amount, and perhaps is exceeded by the elastic element; but, on the other hand, wherever fibrillated tissue is present to any extent, notwithstanding the presence of elastica in large amount, there is also present equally large or larger amounts of white fibrous tissue.

**CONCLUSIONS.** 1. In all forms of cirrhosis the white fibrous tissue is increased.

2. Along with the increase of white fibrous tissue there is a new formation of elastic tissue. This new elastic tissue is derived

from pre-existing tissue in the adventitia of bloodvessels and the hepatic capsule.

3. Both white fibrous tissue and elastic tissue, in all forms of cirrhosis, may penetrate into the lobules. This penetration takes place along the line of capillary walls or follows the architecture of the reticulum. The chief distinctions between the histology of atrophic and hypertrophic cirrhosis depends upon the degree of extralobular growth and the freedom with which the lobules are invaded. In hypertrophic cirrhosis there would appear to be less interlobular growth and an earlier and finer intralobular growth.

4. The alterations in the reticulum, *per se*, consist, as far as can be made out at present, of hypertrophy rather than hyperplasia of the fibers. It is still uncertain whether any of the differential methods now in use suffice to distinguish between the reticulum and certain fibers derived from the white fibrous tissue of the periphery of the lobules.

May 24, 1900.

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### The Effect of Cold Upon the Vitality of the Bacilli of Bubonic Plague.

HIDAYO NOGUCHI, M.D.,  
TOKIO, JAPAN.

(Communicated through SIMON FLEXNER, M.D.)

In the autumn of 1899 a Japanese Medical Commission was dispatched, at the request of the International Sanitary Board, to New Chwang, a port in the northern portion of China, for the purpose of combating the plague which had prevailed there since the end of the summer.

At the time of our arrival the winter season was approaching and the epidemic diminishing in severity, so that I was able to see only 11 cases, 7 of which were of the pneumonic and 4 of the bubonic form.

The winter of our stay was of the severe Manchurian type, and the river Laio was sealed with ice. The conditions seemed favor-

able for testing the resisting power of the plague bacilli against cold. Hitherto the experiments respecting the resistance of these organisms had been made for the greater part with heat, though a few of these, of an unsatisfactory character, had been made with extremes of cold. Inasmuch as I utilized the natural cold, it was manifestly impossible to obtain a constancy of temperature, so that I noted the extremes, viz.: the maximum and the minimum of the days on which the experiments were performed. The thermometers employed were obtained from the Custom House, consisting of two sets; these were observed at intervals of three hours.

The material used for the experiments was obtained from two cases, one of which was of the pure pneumonic type, and the other also pneumonic but associated with buboes.

Pure culture upon agar-agar and bouillon which had been incubated for forty-eight hours at 35° C. were exposed to cold. In addition to these experiments, a third series in which the semi-dry material was smeared upon cover-glasses was employed. The several kinds of material were exposed in a place free from the sun. A determination of the viability was made by transplanting, out of each culture, large blocks of colonies upon culture media, which were placed in the incubator.

The experiments covered a period of three weeks, from January 9th to 29th, 1900. One of the necessary conditions of the experiments is the demonstration of the agar as suitable to the growth of the bacilli. This precaution was not omitted. In the case of the smear preparations, the cover-glasses were placed in nutrient media immediately after the exposure. The following table gives the results of the experiments:

Date.	Temperature.		Exposure time.	Results.		
			Days.	A.	B.	C.
January 9 . . . .	—4° F.	—15 5° C.	1	+	+	+
10 . . . .	—1	—18.5	2	+	+	+
11 . . . .	—7	—21.5	3	+	+	+
12 . . . .	—4	—20	4	+	+	+
13 . . . .	—9	—23	5	+	+	+
14 . . . .	—10	—23.5	6	+	+	+
15 . . . .	—7	—21.5	7	+	+	+
16 . . . .	—9	—23	8	+	+	+
17 . . . .	—10	—23.5	9	+	+	+
18 . . . .	—0	—18	10	+	+	+
19 . . . .	10	—12				
20 . . . .	—2	—19				
21 . . . .	—2	—19				
22 . . . .	—6	—21	2 weeks	+	+	+
23 . . . .	—5	—20.5				
24 . . . .	—10	—23.5				
25 . . . .	—8	—22				
26 . . . .	—11	—24				
27 . . . .	—8	—22				
28 . . . .	—8	—22				
29 . . . .	7	—14	3 weeks	+	+	+

From these experiments it can be concluded that whereas the plague bacilli are devitalized at 60° C., that is 20° above the maximum temperature of development, a corresponding extreme below the minimum limit of multiplication, viz.: —20° C., does not cause a similar destruction.

Incidentally I have experimented to determine the effect of drying upon the vitality, and have found that a temperature of 35° C. continued for twenty-four hours suffices to kill the bacilli when suspended within a thin stratum upon cover-glasses.

The conclusion to be drawn is that plague bacilli contained within fluid or solid media, or in the semi-dried state, survive temperatures ranging from —5° C. to —24° C. after an exposure of at least three weeks.

*October 25, 1900.*

### Cerebral Hemorrhage.

AUGUSTUS A. ESHNER, M.D.

J. C., a white woman, forty years old, was admitted to the Philadelphia Hospital on August 8, 1900, presenting left hemiplegia of three days' standing, which had developed after what was described

as a "fainting spell," unattended with loss of consciousness or fall. The face was not involved, nor was the tongue. Urine and feces were voided involuntarily. The patient exhibited also delusions and hallucinations, and she talked a good deal and incoherently. The pupils were equal and reacted to light. The reflexes could not be elicited on the left side, and sensibility appeared at first to be abolished, and subsequently delayed. Examination of the urine disclosed on one occasion the presence of albumin and granular casts, and on another occasion no abnormal condition.

The temperature fluctuated for a few days between  $100^{\circ}$  and  $102.5^{\circ}$ , then for a few days more between  $99^{\circ}$  and  $101^{\circ}$ , becoming normal on the ninth day and subnormal on the thirteenth day, at which level it continued, with exacerbations to the normal on the day of death. Toward the termination of the case the pulse and respiration became accelerated.

Death resulted fifteen days after admission. On postmortem examination the body was found to be that of an obese, muscular woman. The left ventricle was hypertrophied, but otherwise the heart was normal. The kidneys were fatty and the seat of cysts, and the cortex was thickened. The calvarium, the dura, and the pia presented nothing noteworthy. Pressure on the brain developed slight, deep-seated fluctuation, while pressure on the corpus callosum developed marked fluctuation. Both ventricles, when opened, were found enormously dilated. No gross lesion was found in the left hemisphere, but in the right was a large hemorrhage the size of an egg, destroying the basal ganglia, and showing in part distinctly through the ependyma.

*October 25, 1900.*

# Proceedings

of the

## Pathological Society of Philadelphia.

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### DR. ALFRED STILLÉ.

Resolution adopted by the Pathological Society of Philadelphia  
at its stated meeting held November 8, 1900:

*Resolved*, That in the death of Dr. Alfred Stillé, one of its  
Founders and early Presidents, the Pathological Society of Phila-  
delphia has lost a member who was pre-eminent in his day in  
claiming for pathology a position of fundamental importance in  
the study of medicine, and who lost no opportunity of emphasizing  
this belief in his lectures and by his writings.

That the profession of the United States has lost a member  
whose great learning, scholarly accomplishments, and clear and  
elegant diction placed him easily foremost among the medical  
authors of the period in which he lived, and his writings among  
the classics of medicine.

That a copy of these resolutions be sent to the family of Dr.  
Stillé.

JAMES TYSON,  
J. H. MUSSER,  
CHARLES W. DULLES,  
Committee.

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DR. J. M. DA COSTA.

At a stated meeting of the Pathological Society of Philadelphia, held November 8, 1900, the following minute, presented by a committee appointed by the President, and consisting of Drs. Arthur V. Meigs, J. C. Wilson, and Henry Morris, was adopted, and a copy ordered sent to Mr. Charles F. Da Costa.

The Pathological Society of Philadelphia has received with profound sorrow the announcement of the death of its late eminent member, Professor J. M. Da Costa.

Dr. Da Costa was one of the founders of the Society, and always maintained a deep interest in its work and welfare. He served as its first Secretary, and in 1864, 1865, and 1866 he was its President. Like most of those who have attained distinction in clinical medicine, he devoted much time during the early years of his career to the study of pathology. His success as a clinical teacher and as a practitioner and his reputation as a diagnostician placed him in the foremost rank among the physicians of the last half of the nineteenth century. To brilliant professional attainments he added great learning and rare literary ability. His influence in professional life, and particularly among the young men with whom he came in contact, was the best.

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Experimental Tuberculosis in Cats.

JOSEPH MCFARLAND, M.D.

The well-known fact that feline animals rarely suffer from spontaneous tuberculosis, and that among captive animals, which suffer far more from tuberculosis than others, wild cats are rarely infected, suggested to me that it would be interesting to observe the effects of experimental inoculation with several different tubercle bacilli. For the purpose three bacilli were selected, the first being an avian tubercle bacillus, which came to me from Dr. M. P. Ravenel, who secured it from Professor Westbrook, of Minneapolis. Further than this I do not know the lineage of the organism. It



has the morphologic and tinctorial characteristics of the tubercle bacillus, but grows on simple nutrient agar-agar as well as upon glycerin agar-agar. Its effects upon guinea-pigs and rabbits have not been studied since I have been possessed of it. The second was a tubercle bacillus isolated from human tuberculous sputum by Professor Theobald Smith, of Harvard University. It was of low-grade virulence. The third organism was a bovine tubercle bacillus of marked virulence, also isolated by Professor Smith. All three organisms had been frequently transplanted to fresh glycerin agar-agar in the laboratory, and were kept constantly at 37° C. in the dark.

On May 1, 1900, a bouillon suspension of each culture was made, and one cubic centimeter administered by intraperitoneal injection to three kittens respectively. The kittens had been born in the laboratory, were apparently perfectly healthy, and were about two-thirds grown at the time of inoculation. The kittens all lived until July 24, 1900, when it became desirable to get rid of them, and they were chloroformed. This unnatural death somewhat limits the importance of the experiment, as it is not impossible that all the cats might have lived much longer and recovered. However, before their destruction it had been noticed that the kitten which received the bovine bacillus did not grow as fast as its fellows, seemed weak, had a large belly, and was not well.

Careful necropsies were made upon the animals, the organs being studied macroscopically and microscopically. The results were as follows:

Kitten I. White and gray, gray about the eyes. Infected with the avian bacillus. The cat was well developed, had been well, and was apparently in good condition.

The necropsy showed the abdominal and thoracic organs to be quite normal in appearance. Indeed, the only abnormalities present to the unaided eye were a cheesy mass the size of a small pea in the spleen, some enlarged retroperitoneal glands, and a mottled appearance of the surface of the kidneys, suggesting the presence of subcapsular tubercles.

When the microscopic examination was made it was found that the splenic lesion was tuberculous and contained myriads of bacilli which could be easily demonstrated by Gabbet's method. The en-

largement of the retroperitoneal glands may have resulted from the infection, but there were no tubercles and no bacilli present. The mottling of the kidneys seemed to depend in part upon irregularities in the circulation. The microscope revealed small tubercles, chiefly in the subcapsular zone and labyrinth of the kidney.

Kitten II. Black. Infected with the human bacillus. The cat was well-developed, had been well, and seemed to be in good condition. When the body was opened the abdominal and thoracic organs were for the most part normal. There were enlarged retroperitoneal lymphatic glands, and, as in the other case, the kidneys presented a mottled appearance, as if numerous cortical tubercles were present.

When studied microscopically it was found that the kidneys contained considerable numbers of subcapsular tubercles and round-cell infiltrations descending from the cortical areas along the medullary rays.

Either the tubercle bacilli present were very few in number, or our methods were faulty; but no organisms were demonstrable. The tubercles were quite typical in appearance, in many of them distinct giant cells being present.

Kitten III. Gray and white, white about the eyes. Infected with the bovine bacillus. The cat was small in size, the coat rough, the belly large. It had been observed for some time that the animal was unwell.

When the abdomen was opened it was found to contain a considerable amount of pus of a thick, curdy character. The pus was at once stained for tubercle bacilli, but none were found. There was a wide-spread tuberculosis of the peritoneum and viscera. Both parietal and visceral peritoneums were studded with tubercles, here and there aggregated in good-sized groups. In the great omentum there was a tuberculous mass as large as a pigeon's egg. The mesentery contained many tubercles, and its glands were enlarged and tuberculous. The liver was enlarged, fatty infiltrated, focally hemorrhagic, and evidently occupied by richly distributed tubercles. The spleen was much enlarged, its capsule thickened, and its substance tuberculous and hyperplastic. The kidneys showed grayish nodules with all the appearances of tubercles.

The disease was not confined to the abdomen, but had also spread to the thorax and the lungs, and also the pleura contained tubercles. The whole picture was typical of wide-spread chronic tuberculosis.

The microscopic study of the organs confirmed fully the naked-eye appearances, and tubercles were found in all the organs, bacilli being demonstrated in the greater number of them.

The histologic changes seem to be more destructive than might be inferred from the chronicity of the case, the amount of leukocytic infiltration and necrosis being considerable.

The experiment proves, therefore, that it is possible to infect young cats with avian, human, and bovine tuberculosis by intraperitoneal inoculation. It seems to indicate that the probability of fatal infection with the avian and human bacilli is slight, as in the cases experimented upon the progress of the disease was either very slow or had in large part recovered—a bare probability, as the organs were too normal in appearance to warrant the view that they had once been tuberculous.

The bovine bacillus, which, according to Smith's experiments, is much more likely to be virulent, and was much more virulent than either of the others employed, is capable of bringing about most extensive tuberculous disease.

It is interesting to observe that in the animals infected with the avian and human bacilli, in which there were so few changes, the disease had localized itself largely in the kidneys, while in the animal infected with the bovine bacillus and showing wide-spread lesions the kidneys were much less affected. This is too suggestive to pass without remark, though it may have been a purely accidental occurrence. It is not impossible that the bacilli being taken to the circulation by the lymphatics, and finding no suitable soil for growth in the tissues, were, on their way to elimination by the kidneys, met with some unexpected obstacle and developed in these organs. This speculation, however, carries with it all the doubts that surround the excretion of bacteria by the kidneys, and is offered more as a suggestion than as an explanation.

*September 27, 1900.*

## The Dissemination of Tubercle Bacilli by Cows in Coughing a Possible Source of Contagion.

MAZŮCK P. RAVENEL, M.D.

*(From the Laboratory of the State Live-stock Sanitary Board of Pennsylvania.)*

At the present day it is the general opinion of investigators and physicians that the chief method of the dissemination of tuberculosis is the inhalation of dried tuberculous sputum, which becomes pulverized, and is carried about by currents of air or raised from its resting-place in the cracks of floors—for instance, through sweeping and such like processes. The experiments of Cornet, made under the direction of Koch, are strongly corroborative of this opinion. The habit of indiscriminate spitting by persons suffering from consumption has until very recently been accepted, then, as the chief means by which the contagion was spread, and such indeed is the general opinion held to-day. Flügge has recently taken exception to this opinion, and holds that the spread of tuberculosis is due mainly to the inhalation of minute particles of sputum which is brought to a state of fine division during the act of coughing. He believes that these minute particles float in the air for some time and may be carried by very slight currents. He brought forward as confirmatory of this opinion experiments by himself and his assistant, which are now well known. In this country Klebs has by similar experiments shown that during the act of coughing minute particles of sputum, oftentimes containing tubercle bacilli, are thrown out. Dr. Curry, of Boston (*Boston Medical and Surgical Journal*, October, 1898, vol. cxxxix., No. 15), at the suggestion of Klebs, carried out experiments in twelve cases of tuberculosis with a view of determining what degree of danger there might be from this source. He examined the mouth-fluid of patients whose sputum revealed the presence of tubercle bacilli, and in nine out of twelve cases the bacilli were found at some time during the day, though usually in very small numbers. In three of the cases many bacilli were found at nearly every examination. As a rule they were most plentiful in the early morning. He also suspended glass plates before these

patients at distances of from one to three feet. By this method one-half of the cases gave negative results. All of them, however, had low cough and were in the habit of keeping the lips closed during coughing. Of the six patients who gave positive results, all had a loud cough and kept the mouth open during coughing. He concludes from his experiments that there is not only a possible, but even a probable danger from this source, but he considers that Flügge has greatly exaggerated this danger. He very aptly calls attention to a point which seems to have escaped Flügge entirely—namely, that these small particles of sputum are likely rapidly to become dry, in which condition, of course, they act just as so much dried infectious sputum. Wherever particles of sputum which contain virulent tubercle bacilli are thrown out a possible source of danger must inevitably be recognized.

In a series of studies having for their object the relation of bovine tuberculosis to human health, I was led to see if it were not possible that cows in the act of coughing would likewise expel small particles of tubercular material rich in tubercle bacilli. The opinion is widely accepted that cows swallow all their sputum and do not eject it to any extent. Various methods for the collection of sputum from the trachea and larynx of cows have been tried, with the idea of using it for diagnostic purposes. Pols proposed the insertion of a canula into the trachea for the collection of mucus, but this has not proved satisfactory. Nocard has suggested the injection of veratrin or eserine in order to increase secretion from the bronchial tube, but this likewise has been unsuccessful. The use of a swab inserted down the trachea by means of a long handle, as proposed by Greffier, has given better results. The method used in my experiments has been much more simple and easily carried out. It consists in the use of an ordinary nose-bag, near the bottom of which is placed a shelf of soft pine wood, which is sterilized by steam heat each time before using. Such a nose-bag may be left on the animal for several hours at a time, the amount of material collected varying greatly in different animals and in the same animal from day to day. The smallest particles ejected by the cow during the act of coughing adhere to this piece of soft pine wood, which absorbs most of the fluid portion, leaving the more solid particles standing in relief,

so that they can be easily detected by the naked eye or by a low magnifying glass. From this they may be removed with a platinum needle to a cover-slip and examined under the microscope. By this means I have been able to detect tubercle bacilli in the bronchial secretions of every tuberculous cow in which it has been tried. In one animal the amount of secretion was exceedingly minute, and even after the nose-bag had been kept on her for from three and a half to four hours there would often be only a few particles of matter not larger than the head of a pin, but they were almost always exceedingly rich in tubercle bacilli. In this way what might be expected theoretically has been practically demonstrated—namely, that in the act of coughing cows as well as men atomize, so to speak, their sputum and project it into the air in minute particles, which may float for a considerable period of time. Secretion collected in this way has been inoculated into the peritoneal cavity of guinea-pigs, and even when the bacilli could not be demonstrated under the microscope a considerable portion of positive results have been obtained. I do not mean to advocate this method as a means of diagnosis, although my experiments warrant me in believing that tubercle bacilli can always be found in the sputum of tuberculous animals at some time, but doubtless in early cases it would require a large number of examinations, and with the well-established use of tuberculin it would seem unnecessary to resort to this means. The danger of infection by means of this atomized sputum, as far as mankind goes, is practically confined to those in constant contact with the animals, but for other animals in the same stable these particles must be considered a source of danger.

Of thirty-four examinations carried out on five different animals, tubercle bacilli were detected by microscopic examination twenty times. The number of bacilli found varied greatly, but one of the cows constantly coughed up a tenacious mucus in which the numbers approached those seen in human sputum from advanced cases.

During a period of time extending over forty-three days mucus from two cows was collected by means of the nose-bag on eighteen days, and inoculated into the peritoneal cavity of forty-five guinea-pigs. Of these, twenty-three died within a few days—most

of them from peritonitis, at a period too early for the development of tubercular lesions. Subtracting these, we have remaining twenty-two animals, eleven of which, or 50 per cent., became markedly tuberculous.

By means of a special nose-bag guinea-pigs were exposed directly to the breath of cows in the sputum of which tubercle bacilli had been found. Fourteen pigs were exposed for varying periods of time, as follows:

2 guinea-pigs for 2 hours on 1 day.					2 guinea-pigs for 5 hours on 2 days.				
2	"	"	2½	"	1	"	2	"	"
2	"	"	3	"	1	"	2	"	"
2	"	"	3	"	1	"	2	"	"

These animals were killed after several weeks, but no evidence of tuberculosis could be detected in any of them.

The cows on which the examinations were carried out were all marked cases of tuberculosis, though only one was in the last stages of the disease. One animal which gave a large proportion of positive results lived for more than two years after the experiment.

*November 8, 1900.*

## Two Cases of Glioma of the Retina.

G. E. DE SCHWEINITZ, M.D.,

AND

E. A. SHUMWAY, M.D.

As a certain amount of interest always attaches itself to glioma, the following cases are deemed worthy of record:

CASE I.—L. E., a male Hebrew child, aged three and a half years, was brought to one of us (Dr. de Schweinitz) on the 29th of June, 1900, for an opinion on the left eye, which was blind, painful, and prominent.

*History.* There was nothing important in the clinical history of the child, who is the only one, and who had been in sturdy health until recently, when great restlessness developed, particularly at night, doubtless due to pain in the affected eye. The right eye was normal in all respects, as far as could be ascertained

by ophthalmoscopic examination. Eight months prior to his visit, that is to say, when the child was not yet three years old, a white spot appeared in the pupil of the left eye, and the child was taken to several of the hospitals of this city, but failed to follow the advice there given. Within the last few months the eyeball became distended and masses began to appear in the orbit.

Examination showed a greatly enlarged eyeball, a wide pupil, behind which all interior examination was obscured by the cataractous lens. The episcleral and posterior conjunctival vessels were enormously enlarged and distended. The tension of the eyeball was  $+3$ . Below and to the outer side, and apparently adherent to the floor of the orbit, were several large episcleral nodules. The diagnosis of intraocular growth, almost certainly glioma, in the stage of extraocular tumor formation, was readily made, and evisceration of the contents of the orbit was advised. This operation was performed on the 2d of July at the Jefferson College Hospital, the entire contents of the orbit with the periorbital tissue being removed in a single mass.

Convalescence from this operation was uneventful, and the child was dismissed from the hospital about the 15th of August. There is no note that there was any recurrence of the growth at this time. On the 15th of September of the present year the child, after a day or two of great restlessness, was seized with convulsions and was hurriedly conveyed to the Pennsylvania Hospital. The convulsions ceased very soon, but recurred the same evening, when the child was again taken to this hospital, where he died in a few hours. The note on the book of the hospital is the following: "Unilateral spasms, clonic in character, and coming on in paroxysms; internal strabismus of the right eye; twitching of the fingers and toes; rapid, feeble pulse; marked cyanosis; hurried respiration." Unfortunately an autopsy was not obtained. On interviewing the father as to recurrence *in loco*, it was ascertained from him that the orbital cavity had healed completely; but that a small button, as he expressed it, was visible at the bottom of the pit. This may or may not have been a recurrence, as it is common to find a small mass of granulation in the orbit after exenteration, and we are inclined to think that this should be so regarded.



The clinical symptoms point to intracranial involvement or metastasis. This is rendered the more likely, inasmuch as the brain, after the cranial and facial bones, is the most frequent region for the appearance of metastatic deposits.

The eyeball was placed in a 5 per cent. formalin solution, and subsequently cut in two, one half being mounted in glycerin jelly, and the other embedded in celloidin, and cut in sections parallel to a horizontal plane passing through the cornea and optic nerve. Its anteroposterior diameter measures 26 mm., the vertical 22 mm., and the horizontal 22 mm. The posterior half is filled with a grayish-white mass, which has broken through the sclera, and forms an extraocular nodule, closely investing the optic nerve at its entrance into the ball. The anterior part of the tumor mass stains less well than the posterior. It is composed of a mass of round cells, the majority of which have undergone degeneration, and shows in places dense deposits of lime salts. Certain portions of the growth, especially the better staining ones, show the usual tubular arrangement which glioma cells assume: thick mantles of well-preserved cells surrounding the bloodvessels and projecting into the other masses of cells which have lost their staining power. The two portions are separated partially by the proliferating pigment epithelial layer of the retina, and represent respectively the original retinal growth, and the secondary deposit, in the choroid. The retina is attached as far back as the ora serrata; here it bends abruptly inward, and widens out into the tumor mass. The latter springs from the inner nuclear layer, as the outer nuclear layer continues for a short distance undisturbed. The bloodvessel walls are much thickened, and show hyaline degeneration to a marked degree. The anterior part of the globe shows the effect of the increased tension, all of the tunics being relatively thin. The ciliary processes are stretched forward and are atrophied; there are also marked atrophy of the iris, and a well-developed intercalary staphyloma. The cornea is thinned and staphylomatous, but is otherwise normal. The lens shows beginning cataractous changes in its cortical layers. Both anterior and posterior chambers are quite deep, but the filtration angles are blocked by the firm adhesion of iris and cornea. The optic nerve is replaced partly by the infiltrating tumor cells, which have passed along the

lines of the nervous bundles and also through the intervaginal space. The uninfiltreated part of the nerve shows a conversion of its entire structure into hyaline connective tissue. The sclera is very much thinned, and its fibers are separated by lines of glioma cells. None of the rosetts described by Wintersteiner are present in the tumor. Pieces of orbital tissue were also cut for microscopic examination. They show extensive infiltration with glioma cells; in places this infiltration is diffuse, in others the cells are grouped in dense masses, and exhibit a decided tendency to cell death. In both the orbital and intraocular portions of the growth there are a great many karyokinetic figures. These are especially notable around the bloodvessels, where the cell growth is most rapid. Sections of the lacrimal gland show mononuclear, round-cell infiltration around the bloodvessels, and between the acini, but no glioma cells are present.

CASE II.—E. B., aged nine years, male. Patient of Dr. George E. Rohrer, of Lancaster, Pa. The boy was first seen by Dr. Rohrer in February, 1900, but the ocular symptoms appeared one year before. At this time the eye became weak and watery, and some pain was complained of, but the symptoms subsided in a week's time. Similar attacks recurred, however, and several months later the pupil was found dilated ad maximum, and vision was reduced to zero. In the back part of the eye whitish patches were seen, and, later, the whole of the retina presented a yellowish-white appearance. Despite the occurrence of these attacks, the boy attended school regularly until, at Christmas, the eye began to bulge. When seen by Dr. Rohrer there was marked exophthalmos, the tension of the globe was elevated, and vision was nil. The anterior chamber was filled with a yellowish mass, which prevented any view of the fundus. Enucleation was immediately advised and performed. During the operation an attempt was made to cut well back of the optic nerve entrance, and, as the orbit was involved, the tissue was removed as far as it seemed to be diseased. There was, however, a very rapid recurrence, which soon filled the orbital cavity, and the boy died about three months later.

The eyeball was placed in alcohol at the time of enucleation, and was subsequently frozen and cut in a horizontal plane. The

macroscopic specimens show that the globe is filled with a grayish-white mass, the central part of which is necrotic. In addition to the intraocular mass there is a large extraocular nodule, the sclera running as a narrow band, with a pigmented inner border, between the two portions. The globe has become shrunken and distorted in the alcohol, presenting a ring-shaped depression in the ciliary region, which allows the cornea to project forward in the form of a nipple. The anterior chamber is filled with a yellowish-white mass; the lens is crowded forward in front of the ciliary processes and jams the iris against the cornea at its periphery. The globe measures 24 mm. in its anteroposterior diameter, 21 mm. vertically, and 21 mm. horizontally.

Sections stained with hematoxylin and eosin show macroscopically that the mass is composed of two parts—a poorly staining one, occupying the anterior part of the eyeball, and a well-staining mass posteriorly, which includes the extraocular nodule. The poorly staining portion, when examined under the microscope, is seen to be made up of a mass of necrotic tissue, the greater part of its cells refusing the stain. Here and there are groups of round cells which stain faintly with hematoxylin, the nuclei of which are undergoing fragmentation. In contrast with this mass of unstained tissue the bloodvessels stand out prominently, their lime-infiltrated walls staining dark blue with the hematoxylin. This is evidently the original tumor. The retina can be traced only as a line of degenerated tissue, extending inward from the ora serrata, and the growth has advanced too far to determine the layer of the retina from which it has sprung. The posterior well-staining portion represents the secondary infiltration of the choroid. It shows moderately well the tubular arrangement typical of glioma. The bloodvessel walls have undergone marked hyaline change and the mass is infiltrated with scattered masses of pigment, part of which represent the remains of the stroma cells of the choroid, but the greater part is evidently the result of previous blood extravasation. The sclera is infiltrated, and the optic nerve is entirely replaced by the growing tumor. Anteriorly the ciliary bodies are stretched forward and are quite atrophic. The lens is pushed forward in advance of them; it shows extensive cataractous changes: proliferation of the capsule epithelium, separation of the

fibers by a coagulated fluid, with destruction of individual fibers. The iris is pressed firmly against the corneal periphery, entirely blocking the filtration angle, and is to a high degree atrophic. The cornea is stretched, but is otherwise normal, neither Descemet's nor Bowman's membrane showing any break in its continuity. The mass in the anterior chamber is composed of degenerated glioma cells, only a few retaining their staining power. In no part of the tumor mass are there any of the so-called rosets.

In connection with these cases of glioma of the retina, which present no features distinguishing them from the many cases now on record, it may be well to review the subject of the etiology of the growth in question, especially as there has been little mention in American literature of the very animated discussion that has been called forth on the Continent by Wintersteiner's monograph.<sup>1</sup> For many years the scientific world has been divided into two camps—those defending Virchow's views,<sup>2</sup> that glioma develops from the neuroglia or supporting tissue of the retina—among them Hirschberg,<sup>3</sup> Iwanoff,<sup>4</sup> Knapp,<sup>5</sup> etc.; and, on the other hand, those who take the ground that it is a round-cell sarcoma, or plexiform, or tubular angiosarcoma (Delafield,<sup>6</sup> Vetsch,<sup>7</sup> Straub,<sup>8</sup> Mazza,<sup>9</sup> Van Duyse,<sup>10</sup> Becker<sup>11</sup>). Virchow's stand-point has recently received strong support from Greef,<sup>12</sup> who, by means of the Golgi-Cajal silver method, was able to show the presence of long protoplasmic processes in connection with the cells, thus demonstrating their neuroglial character. These results were confirmed by Hertel,<sup>13</sup> although he did not succeed when employing the Weigert neuroglia method. Both Greef and Hertel found also numerous ganglion cells, and the former has proposed to call the growth neuroglioma ganglionare, following Klebs,<sup>14</sup> who had chosen the name of neuroglioma, not only for the retinal tumors, but also for the gliomata of the central nervous system.

Wintersteiner, however, lays especial weight upon the epithelial rosets, described by Flexner,<sup>15</sup> Eisenlohr,<sup>16</sup> Becker,<sup>11</sup> and Van Duyse,<sup>10</sup> which he found in 11 out of 26 cases of glioma investigated by him. These peculiar structures consist of closed or partly closed rings of 10 to 12 narrow, wedge-shaped, cylindric cells, the lumen of the roset being lined by a distinct basement

membrane. In places, rod-shaped protoplasmic processes extend into the lumen, through the basal membrane. He considers that these cells, with their processes, are rudimentary rod and cone cells, that the basal membrane represents the *limitans externa retinae*; and as he found them in a beginning glioma nodule in the external nuclear layer, where they could not be present normally, he believes that glioma arises from embryonally misplaced cells of the neuro-epithelial layer of the retina. He described these roset formations in two malformed eyes, which were free from tumor formation, and in one case he was able to show a direct transition of the cells to the rod-cone fibers and to the *limitans externa retinae*. He further mentions that Salzmann has also described similar rosets in an eye with a conus below the optic nerve entrance, and as clinical observation permits no doubt as to the influence of congenital disturbances upon the production of the tumor, Wintersteiner suggests the name of neuro-epithelioma *retinae*. That the rosets were found in only one-third of his cases was not considered important by him, as it is not necessary that the misplaced cells should, in every case, reach the height of development necessary to produce the fully formed rosets. He does not deny the presence of glia cells in the growth, but claims that they do not decide the nature of the growth, because such cells are present normally, and the supporting tissue may be increased without, however, constituting the essential element of the tumor.

On the other hand, Ginsberg<sup>17</sup> has described groups of cells in the displaced and partly detached retina, in the micro-ophthalmic eye of a new-born child, which showed transition to the cells of the *pars ciliaris retinae*. Such rosets have also been found in micro-ophthalmic, or otherwise malformed eyes, by Dötsch,<sup>18</sup> Bernheimer,<sup>19</sup> Pichler,<sup>20</sup> Bock,<sup>21</sup> Rubinski,<sup>22</sup> and Helfreich.<sup>23</sup> Ginsberg thinks that Wintersteiner's claim that the neuro-epithelium is involved in the formation of the roset has not been proven, but that they more closely resemble the cells of the *pars ciliaris retinae*, and as the latter are found before the division of the cells of the future retina into spongioblasts and neuroblasts, he believes that the origin of the growth must be from cells which have remained upon this low stage of embryologic development. In any

case the cells composing the tumor are epiblastic in origin, and not mesoblastic, so he suggests the name "carcinoma retinae" in place of neuroepithelioma retinae. Pichler's work confirms that of Ginsberg, and his conclusions are identical.

As Axenfeld<sup>24</sup> remarks in his review of the subject in Lubarsch and Ostertag's *Ergebnisse* (1898), from which we have freely quoted, the purely sarcomatous conception of the tumor has certainly lost very much ground. Wintersteiner argues that its origin, in many instances, from the outer nuclear layer, where there are no mesodermal elements, precludes the use of the term sarcoma. Treacher Collins<sup>25</sup> also expresses himself strongly against this term. He shows that in the fourth fetal month the retina is composed of the same cells as those in glioma. That this morphologic proof of the epithelial nature of the growth is further supported by the clinical facts that glioma appears usually before the sixth year, that metastases in the liver are rare,\* while the propagation in the lymph channels is the usual one; that sarcoma is never bilateral, and that histologically the glioma cells are poorer in protoplasm, show fine protoplasmic processes, and are much more inclined to degenerate.

The discussion upon the subject is evidently not ended, but the newer work points toward the greater probability of the epithelial character of the growth. If the findings of Greef and Hertel be still further confirmed, especially by other methods, its neuroglial origin must be admitted. The silver method, however, is too uncertain in its results, and we must consider this proof as not yet thoroughly established.

\* Metastases in the liver are not exactly rare. Thus, in a recent paper by F. M. Wilson and Edgar S. Thompson (*Archives of Ophthalmology*, January, 1900), there is recorded a case of glioma of the retina and brain metastasis with autopsy, and a review of the literature. In a total number of 530 cases metastases were recorded 61 times, and of these 61, 7 appeared in the liver, the only other regions of the body more frequently affected by metastatic deposits being the cranial and facial bones, the brain, the lymphatic glands, and the parotid gland.

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*November 22, 1900.*

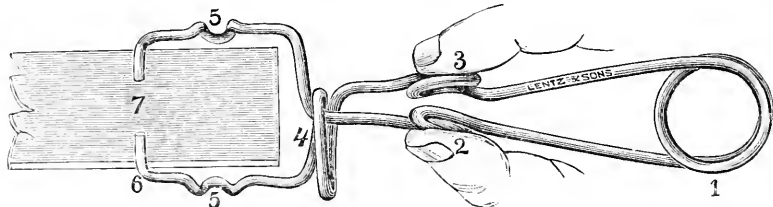
## A Combined Slide and Cover-glass Forceps.

L. NAPOLEON BOSTON.

The forceps I present for your consideration this evening is by no means new, but has been in use by me for the past two years, during which time its application to general microscopy has pointed out its many defects. To perfect this forceps in every possible way it has been necessary to have a forceps constructed showing each of the many modifications which experience alone could suggest. A study of the various developmental stages of the forceps

I now present is of interest, and the need of such a forceps has long been apparent to every laboratory worker. Heretofore the writer has employed two instruments for this purpose, viz., a Stewart cover-glass forceps and his own slide forceps (*Journal of the American Medical Association*, September 8, 1900, p. 641).

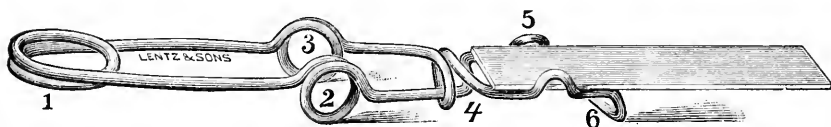
FIG. 1.



At the suggestions of Drs. W. M. L. Coplin and E. B. Wenner I have modified the said slide forceps so as to give it the double function of both a slide and cover-glass holder, and have adjusted the lateral clamps (5) so as to enable one to grasp the slide from off the table with the forceps. (Fig. 1.)

This forceps is made from a continuous piece of brass wire, which is nickel-plated. The accompanying figures will serve to

FIG. 2.



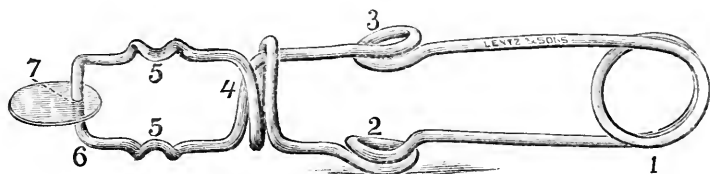
illustrate the forceps in the act of picking the slide from off the table (1), and with the slide locked in position (2); while Fig. 3 represents it as a cover-glass forceps.

It will be seen that the wire is coiled so (1) as to form a spring which serves to hold either slide or cover-glass within the jaws of the forceps. The left lateral coil (2) is slightly flattened to form a firm rest for the forceps when the cover-glass is in position (Fig. 3), and with its fellow coil (3) rests are formed to support the forceps when the slide is in position (Fig. 2). These coils also serve as



convenient places for the thumb and index finger during manipulation. The coil (4) at the base of the jaws is simply to hold them in position. The lateral clamps (5) at the center of each jaw are bevelled so that in springing against the margins of the slide it is lifted from the surface on which it rests and firmly fixed between the clamps. The inner surface of this clamp is provided with a groove so as to accommodate slides of various thicknesses. Beyond this point the wire supports the slide, and at 6 it is bent to form a support for the forceps when the slide is locked in position (Fig. 2). At this point the two ends of the wire are carried inward to meet at the center of the jaws (7), and between these points the cover-glass is held (Fig. 3).

FIG. 3.



By this forceps the slide is lifted from the table, properly adjusted within the forceps' jaws, so as to make its surface level, and thus preventing liquid from changing its position when placed on the slide—by the use of one hand—(Figs. 1 and 2) a heretofore unaccomplished end by a slide forceps. A double value is attached to this forceps in that it is equally serviceable as a cover-glass holder, necessitating but a single instrument for general laboratory work.

October 25, 1900.

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Improved Drawing Eye-piece. New Microscope Stand. New Microtome Clamp. Improved Knife Case. Improved Dissecting Microscope.

W. M. L. COPLIN, M.D.

Dr. Coplin showed (1) a modification of a drawing eye-piece described by Leiss (*Zeitschrift für Wissenschaftliche Mikroskopie*, 1895, xii.). The modification consisted in arranging the color

glasses in attached discs which rendered them easily used and prevented their loss and accidental breakage.

(2) A Dölken microscope stand with modified form of Leitz mechanic stage. The advantages claimed for the combined instruments are (*a*) the extremely large stage, with area for examination of plates and large brain sections, (*b*) mechanic stage movement, covering an area of two and a half inches vertical, and a like distance horizontally.

(3) A new clamp for the Minot microtome, permitting of permanent orientation of objects on the block which is held in the new clamp.

(4) Case for Minot knives, which prevents the edge from coming in contact with anything liable to dull them.

(5) Dissecting microscope with rotating lens-carrier so arranged as to deliver lenses in focus and to permit of use in movement of lenses in searching large fields.

*November 8, 1900.*

# Proceedings

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### The Pathology of the Skin in Scarlet Fever.

J. F. SCHAMBERG, M.D.

The pathology of the skin in scarlatina has been investigated by Kaposi, Klein, Neumann, Delafield and Prudden, Unna, Pearce, and others. They all agree, in the main, as regards their findings. There is dilatation of bloodvessels and lymphatics; an infiltration of lymphoid cells and polymorphonuclear leukocytes into the papillary layer; later, an invasion of the rete mucosum by leukocytes; mitosis and proliferation of the deeper rete cells. Neumann mentions slight proliferation of cells about the hair follicles.

All of these observers evidently excised for examination areas of smooth skin. The sections referred to in this paper represent papules, puncta, vesicles, etc., as well as the erythematous rash surrounding them. My results are in accord with those above quoted; but, in addition, I have attempted to describe the histopathology of these elements of the eruption.

A brief clinical reference to these lesions may advantageously preface the histologic description. Upon close inspection the rash of scarlet fever is seen to be made up of small, deep-red puncta surrounded by erythematous areolæ of a somewhat brighter hue. When the areolæ coalesce, as is usually the case, a diffuse eruption is presented. At times, however, there is some intervening normal skin, giving the rash a more or less speckled appearance. Many scarlatina rashes exhibit small pin-point to pin-head sized elevations occurring for the greater part at the sites of

hair follicles. This condition was termed by the older writers "scarlatina papulosa." In addition to these elevations, an appearance not infrequently noted is a general "goose-flesh" condition of the skin, bearing a close resemblance to the "cutis anserina" evoked by exposure of the normal skin to either extreme of temperature. The goose-flesh papules of scarlet fever differ, however, in their tendency to persist for some days throughout the course of the rash.

Small discrete, pin-head sized, conical vesicles are commonly seen in scarlatina, particularly about the chest, abdomen, and mons veneris. To this the term "scarlatina miliaris" or "vesicularis" has been given. In about 20 per cent. of all cases and 50 per cent. of well-marked eruptions, vesicles are visible if looked for. In a large number of the remaining cases they can only be seen by the closest scrutiny of the skin under the best possible illumination. Finally, there are some which cannot be seen with the naked eye, but are demonstrable under the microscope. In rare cases of scarlatina the vesicular element of the rash may be so marked as to deceive the physician as to the nature of the disease.

The desquamation upon the trunk in scarlet fever is first visible as pin-point, powdery scales representing the summits of desiccated vesicles. In a day or two the scale is cast off, leaving a small jagged ring of desquamation. The horny layer of the epidermis is now lifted off by centrifugal extension of these rings, which grow constantly larger. On meeting enlarging rings of neighboring lesions they produce gyrate and geographic configurations resembling the contours of a map.

The histopathologic data herewith presented are based upon a study of thirteen specimens of the skin removed during life from twelve cases of scarlet fever. The skin was excised by means of a skin punch, after previous injection into the subcutaneous tissue of a 1 per cent. solution of cocain. The excisions were performed upon patients representing stages of the disease from the second to the seventh day.

The sections were hardened in successive strengths of alcohol, embedded in paraffin, and stained in hematoxylin-eosin, thionin, eosin-polychrome-methylene-blue, and the Weigert-Gram stains. A brief description of the different specimens is herewith appended, with a clinical note describing the lesions before excision.

CASE I.—J. B., aged six years. Profuse erythematovesicular rash. Redness very vivid and vesicles remarkably numerous. Area showing a pin-head central vesicle, with a hair perforating,

FIG. 1.



Unusually intense desquamation in a severe case of scarlet fever. Ring character of desquamation shown.

and a few smaller peripheral epidermal elevations excised from the trochanteric region. Under low power the section is seen to contain four hair follicles. At the mouth of the central follicle is a large crateriform cup filled with a mass of deeply-stained

leukocytes and epithelial débris. This connects with the lumen of the follicle. The epithelium of the hair follicle is infiltrated with numerous polymorphonuclear leukocytes. To the right of this is another smaller hair follicle which is also the seat of extensive pathologic change. At the surface of this follicle is a small horizontal oval space containing serum and a deeply-stained mass of cells, and covered by the horny layer of the epidermis. The lower half of the follicle is extensively disintegrated by a serous exudate, which has broken into the follicle, separated the epithelial cells, and formed a lake in which may be seen numerous leukocytes. The follicle is furthermore infiltrated with and surrounded by a dense mass of lymphoid cells and polymorphonuclear leukocytes. At the extreme end of the section is another follicle showing a circular space at the surface filled with serum and leukocytes. The middle third of the follicle exhibits a serous and leukocytic invasion which surrounds the hair, which may be seen *in situ*. Between the two follicles just described there is seen a circular vesicle in the epidermis filled with fluid and densely packed with leukocytes. This occupies an area between the horny layer above and the lowermost strata of cells of the rete mucosum. Numerous rete cells are seen detached and floating about in the exudate. The neighboring portions of the Malpighian layer are invaded with polymorphonuclear leukocytes. The specimen shows in general a dilatation of the bloodvessels and lymph spaces, a deep cell infiltration throughout the corium and about the coils of the sweat glands.

CASE II.—S. M., aged seven years. Well-marked rash. Superficial vesicle excised from abdomen on fourth day of disease.

Sections were stained in hematoxylin-eosin and eosin-polychrome-methylene blue. Under lower power the center of the section is seen to be occupied by a vesicle having its seat in the rete mucosum and its roof formed by the horny layer. Directly contiguous to this is a hair follicle, which shows extensive serous exudation and leukocytes in its lower extremity deep in the corium. The papillary layer is the seat of an extensive infiltration of lymphoid cells and polymorphonuclear leukocytes. There is marked dilatation of the papillary bloodvessels which are seen to be filled and surrounded by cell exudate. In sections stained with hematoxylin-

eosin are seen numerous multinucleated perivascular cells with red granular protoplasm. These are eosinophile cells. Sections stained with the eosin-polychrome-methylene blue show numerous mast cells, particularly about the bloodvessels and walls of the hair follicles. The epidermis exhibits a marked invasion of migratory cells, which may be seen at all levels. There are also visible mitotic figures in the prickle cells of the Malpighian layer. The daughter asters are well seen in the lowermost of the cells. These mitoses occupy cells about the center of the mucous layer.

CASE III.—B. S., aged twelve years. At the outset a typical punctiform rash. On the sixth day the patient was seen again and showed a distinct goose-flesh papular appearance. A goose-flesh papule of normal skin tint was excised from the lateral aspect of the chest. Several smaller papules present.

Under low power the center of the section is seen to be occupied by a hair follicle. Smaller follicles are situated at either end. About the central follicle is a well-marked infiltration of lymphoid cells and polymorphonuclear leukocytes. The epithelial cells of the follicle are broken into and pushed aside by a serous and cellular exudate. The same process, omitting the serous effusion, is present in the smaller follicles. The papillary and subpapillary vessels are dilated and filled and surrounded by lymphoid cells. There is a moderate number of oval and stellate mast cells in the neighborhood of the walls of the follicles. In the perivascular infiltration may be seen small numbers of eosinophile cells. Sections stained in hematoxylin-eosin, thionin, and polychrome-methylene blue.

CASE IV.—F. H., aged ten years. Well-marked rash, punctiform, with scattered small vesicles. An area of skin on which was seated a barely discernible vesicle was excised from the side of the chest upon the seventh day. (Lesion is probably a vesicle, but can only be detected upon close scrutiny of the skin.)

Under low power there is seen in the center of the section a superficial hair pocket, the lumen of which is dilated and filled with leukocytic debris. The epithelial walls are disintegrated by an invasion of leukocytes. The papillary layer of the corium is the seat of an intense infiltration of lymphoid cells and polymorphonuclear leukocytes. There is dilatation of the bloodvessels

and lymphatics and a marked perivascular cell infiltration. Leukocytes are visible between the prickle cells of the rete mucosum. Mast cells are present in small numbers. Sections stained in hematoxylin-eosin and eosin-polychrome-methylene blue.

CASE V.—B. C., aged twenty-nine years. Eruption intense, with hemorrhagic tendency. A punctated spot, not disappearing on pressure, excised from right side of the chest on fourth day of the disease. In the center are a hair follicle and sebaceous gland seen in cross section. These are surrounded by an extensive infiltration of polymorphonuclear leukocytes. The papillary bloodvessels are dilated and surrounded by an exudate of lymphoid cells and polymorphonuclear leukocytes, chiefly the latter. The rete mucosum shows leukocytes infiltrated between its cells.

FIG. 2.



Hair follicle showing superficial vesicle, disintegration by severe exudate, and surrounding cell infiltration. Magnified 145 diameters.

CASE VI.—R. O., aged four years. Well-marked eruption. Small epidermal elevation (vesicle) was excised from lateral aspect of the chest on the second day of the disease.

The center of the section is occupied by a hair follicle; in the mouth is seen a vesicle filled with serum and leukocytes. In some



sections the vesicle is shut off from the lumen of the follicles; in others, however, it is seen directly communicating with the lumen, so that there is practically a clear space extending from the horny layer to the base of the follicle. The epithelium of the follicle is disintegrated as a result of serous and cellular infiltration. The walls of the hair follicle are surrounded by an extensive cell infiltration running parallel to the walls. The papillary bloodvessels are enormously distended and are filled and surrounded with lymphoid cells and polymorphonuclear leukocytes. Sections stained with the Weigert-Gram stain were examined for microorganisms, but none were found.

CASE VII.—R. O. Same patient as Case VI. Redness fading. Minute vesicle with scaly summit was excised from the side of the chest on the fortieth day.

The center of the section is occupied by a hair follicle which is surrounded by an intense lymphoid cell and polymorphonuclear leukocyte infiltration. The papillary and subpapillary bloodvessels are dilated and are surrounded by an intense cell exudate. Mast cells are present in small numbers.

CASE VIII.—E. C., aged twenty-five years. Well-marked eruption. Skin infiltrated. Section of skin with small vesicle upon it excised from anterior surface of forearm.

Under low power are visible two large, circumscribed vesicles occupying the rete mucosum, which is cut obliquely and appears to be considerably hypertrophied. The larger of these extends from the horny layer to the lowermost strata of rete cells. It is filled with serum in which are visible densely packed leukocytes. The walls of the vesicle are made up of several layers of flattened rete cells.

The other vesicle occupies an area of the rete mucosum at the nether extremity of a prolongation, and appears almost to be snared off in the corium. There are visible at different places in the upper portion of the rete, in the granular layer, and even in the horny strata, circumscribed masses of leukocytes without serous effusion. It is possible that desiccation has taken place through absorption of the fluid. Polymorphonuclear leukocytes are seen in abundance invading the rete mucosum. The papillary and subpapillary bloodvessels are distended and surrounded by a marked cell infiltration. The entire corium is infiltrated with cells,

many of which appear to be derived from fixed connective-tissue cells. No hair follicles or sebaceous glands are visible in the section.

CASE IX.—M. M., aged twenty-five years. Well-marked rash. Reddish elevated punctum (apparently at the site of a hair follicle) excised from the lateral aspect of chest on the fourth day.

In the center of the section are a hair follicle and sebaceous gland in cross section. The follicle is surrounded by considerable cell infiltration. Many of the cells of the sebaceous glands are undergoing fatty degeneration; their nuclei are shrunken and distorted. The subpapillary bloodvessels are greatly distended and exhibit an intense perivascular infiltration. The lymph spaces are dilated and contain a cell infiltration.

CASE X.—J. N., aged four years. Well-marked eruption. A papule (possibly papulovesicle) excised from the thigh on the second day of the disease.

Under low power there is visible a cell infiltration in the papillary layer and throughout the entire corium. In the center of the section is a hair follicle surrounded by an intense cell infiltration. The sweat coils are likewise infiltrated. No evidence of any vesicle present.

CASE XI.—H. M., aged six years. Well-marked eruption. Section of skin 6 mm. in diameter, upon which were several small puncta but no vesicles, excised from the trochanteric region on the third day.

Section shows an enormous dilatation of the bloodvessels and lymph spaces. These are surrounded with lymphoid cells and polymorphonuclear leukocytes. A large hair follicle in the section is surrounded by a moderate cell infiltration. There is also visible a sweat duct the lumen of which is blocked with endothelial cells. Free blood is seen in many of the lymph spaces.

CASE XII.—R. F., aged four years. Little or no redness present. Small area of skin excised upon which were seated two or three goose-flesh papules. Third day. (Most of the sections lost by accident; but a few examined.)

The papillary layer of the corium shows an infiltration of lymphoid cells, chiefly about the bloodvessels. Bloodvessels and lymph spaces are dilated. No hair follicles present in the sections examined.

CASE XIII.—H. G., aged twenty-two years. On entrance to hospital, deep, diffuse, smooth eruption over the entire body. No visible elevations at this time. On the sixth day redness largely faded. Scattered pin-head translucent vesicles (with difficulty visible). One of these excised from lateral aspect of trunk. Cell infiltration in papillary layer of corium. Dilatation of bloodvessels which are filled and surrounded by lymphoid cells and polymorphonuclear leukocytes. Small number of mast cells and eosinophiles present. No evidence of vesiculation. (It is possible that the central sections, which should have shown the vesicle, were lost in the section-cutting.)

Let us now interpret the clinical lesions in the light of the histopathologic findings. When an area of skin representing the smooth rash is excised, one finds the common phenomena of an acute simple dermatitis. There is dilatation of the bloodvessels, an exudation of lymphoid cells and polymorphonuclear leukocytes into the papillary layer of the corium, with some invasion of the epidermis with migratory cells.

The *goose-flesh papulation* is not a mere temporary condition due to the contraction of the hair muscles, but results from an extensive infiltration in and about the hair follicles, and therefore persists until the inflammatory phenomena subside.

*Papules* represent cellular infiltration, for the greater part, in and about the hair follicles.

*Vesicles* are invariably characterized under the microscope by a lake of serum containing a leukocytic infiltrate. These vesicles may have their seat in the deeper layers of the rete, or they may be intrafollicular, involving the hair follicles. In either case there is a pushing aside and disintegration of the cells of the mucous layer by a fluid exudation from the papillary bloodvessels. The turbidity of the contents of these vesicles is due to this invasion of the leukocytes. In the attempt on the part of nature to eliminate the materies morbi the leukocytic mass travels toward the surface, lifting up the horny layer. In this manner the effete products are thrown off. At this stage, clinically, desiccation of the liquid contents of the vesicles takes place, followed by the appearance of the small powdery scales at their summits.

The *punctated spot* in several sections proved to be a hair follicle

surrounded by marked cell infiltration. It may, however, show merely dilatation of the bloodvessels with intense perivascular cell exudation. The number of puncta examined was too small to form absolute conclusions as to the frequency of their occurrence about hair follicles.

It will be noted that the hair follicles suffer very greatly in the inflammatory process in scarlet fever. It would seem that goose-flesh papules, puncta, and vesicles all occur more frequently about the pilary pockets than elsewhere in the skin. The depth to which these follicles are involved explains the persistence of desquamation. The walls of the hair follicles are made up largely of cells corresponding to the mucous layer of the epidermis. These cells, being disintegrated by the serous and leukocytic infiltration, must be thrown off from the skin. The depth from which these cells are derived necessarily makes the process a slow one. The persistence of the infectivity of the scales, it appears to me, is explicable upon the same ground. There is reason to believe that the infectious principle is contained in the leukocytes or epithelial débris cast off from the skin. Unfortunately but few sections were stained for micro-organisms, and in these none could be discovered with the ordinary stains employed for this purpose.

In none of the sections was there any enlargement of the papillæ, and, therefore, the statement made to the contrary in some text-books would seem to have no basis in fact.

Karyokinetic figures are seen in some sections, and indicate a proliferation of the epidermal cells, which are perhaps stimulated by the leukocytic invasion. The occurrence of second and third desquamation may possibly be due to this cause.

*October 25, 1900.*

#### Note Relative to the Anatomic Parts of the Skin Invaded by the *Microsporon Furfur* in *Tinea Versicolor*.

M. B. HARTZELL, M.D.

It is commonly stated in text-books of dermatology that the fungus concerned in the production of *tinea versicolor*—the *microsporon furfur*—is found only in the corneous layers of the epidermis. According to Kaposi, the hair is never attacked, and the

parasite grows only in the epidermis of the follicular opening. Hyde states that it never by any possibility invades the hair follicle.

In a somewhat hasty survey of the text-books in my possession I have been able to find but a single author who admits that the follicles may be invaded in tinea versicolor. Gadden, quoted by Crocker, says that the follicles of the lanugo hairs may be penetrated by the microsporon.

Some time ago, in making sections of a piece of skin affected by tinea versicolor, I had the good fortune to divide a follicle throughout its length, and, upon staining it with a view to demonstrating the fungus, I was somewhat surprised to find numerous spores deep down in the follicle as well as in the corneous layer. This follicular involvement explains very readily the well-known tendency of this disease to relapse, relapses occurring, no doubt, through the growth of the spores in the follicle which have escaped the action of the parasiticide applied to the surface. A knowledge of the possibility of follicular involvement is of practical use in that it suggests the necessity of using friction in making applications of parasiticide remedies, in order that the follicles may be penetrated.

*November 8, 1900.*

I. Specimen of the Middle Intestine of the Mosquito (*Culex pipiens*), Showing the Zygotes of *Proteosoma* Labbe.

II. Malarial Parasites from a Case of Malarial Hemoglobinuria.

BY ALBERT WOLDERT, M.D.

If one searches through history in regard to the subject of malarial fever it will be found that this disease has received more or less attention since the days of Empedocles, who lived about five hundred years before the date of the Christian era.

It has been stated that one of our grandest men—the one to whom physicians and surgeons everywhere look up with pride—also gave malarial fever his close attention. Even in his day Hippocrates divided intermittent fevers into the quotidian, tertian, and quartan types. At that time, as now, it was known that a residence in a low, damp soil or adjacent to swampy land might

in some way lead to an attack of chills and fevers. It was believed most strenuously that the *materies morbi* of this disease was due to bad air, and that "mal" air gave rise to "mal" blood. In a search through medical history which I made last year I came across a long series of experiments made by an investigator early in the nineteenth century, in which he endeavored to prove that malarial fever was due to the inhalation of certain noxious gases arising from rapid decomposition of vegetable substances.

Klebs and Tommasi Crudelli, in 1879, after having experimented in different ways with the water obtained from the Roman Campagna, announced that they had at last found a bacillus capable of producing malarial fever. This word "bacillus" of malarial fever is even used in our day, but should be abandoned.

Laveran, in 1880, while examining with a low-power lens the blood of a case of intermittent fever, accidentally discovered the flagellated malarial parasite, and soon afterward found the crescent and pigmented spheric forms. The findings of Laveran were soon confirmed everywhere.

The question for investigators was to prove how this parasite gained entrance into the blood. Men believed that the easiest way would be through the respiratory or alimentary tract. However, Crawford, in 1807, and King, in 1883, held to a different belief. According to them the disease was inoculated through the bite of the mosquito.

Patrick Manson a few years ago came to the same belief, and argued the matter so logically that he soon had an enthusiastic supporter in Ronald Ross, at that time Surgeon-Major of the English Army. Of course, there were doubters everywhere, as there should be in every science, but Ross could not be convinced that he was wrong. Therefore, he went from England to India to study this question. Arriving in India, he found that the season for malarial fever was almost over so far as man was concerned, so he turned his attention to pigeons, sparrows, larks, and crows. It was but natural that he should first begin his experiments with the common kind of mosquito—the species of *Culex*—and after months of work discovered nothing. At this stage one cannot but admire the persistence with which he continued his work, right or wrong, in an endeavor to prove his

theory. It was not long before he found a kind of "dapple-wing" mosquito which bit a case of malarial fever containing crescents, and in two of these he, in a report to the Director-General of the Indian Medical Service, dated September 19, 1897, described "some peculiar pigmented cells found by him in August, 1897, which he anticipated were a stage of the malarial parasite in this insect." Later he was able at will to develop these pigmented cells in the *Culex* by allowing them to bite infected birds suffering with proteosoma.

Ross continued his work from March to December of 1898, and the specimen which I have the honor of presenting to you, which has been kindly loaned me, is one of the best of this series. and dated Calcutta, July 12, 1898.

After these results had been obtained by Ross it next became necessary to learn how this micro-organism developed in the tissues of the mosquito, and was thence transferred back to man.

Beginning first with the classification of the malarial parasites, one finds that they belong to the natural order Gymnosporidia—class sporozoa.

Compared with the micro-organisms of most of the other infectious diseases, these parasites may be said to belong to a much higher form of life than in the case of such bacteria as the tubercle bacillus, cholera bacillus, or the bacillus of Sanarelli.

The sporozoa of malarial fever have never yet been cultivated successfully upon artificial culture media, although it was one of the first disease-producing forms discovered. To perpetuate its existence two biologic cycles are necessary—one being completed in the blood of man, the other in the tissues (middle intestine) of the different species of the *Anopheles*. These two biologic cycles do not resemble one another in the least.

In the case of man the parasite in its earlier stage is found in the peripheral blood, in the form of a very small hyaline actively ameboid body, which later grows at the expense of the red blood disc, and in which it develops spores. These spores subsequently rupture the erythrocyte and at once re-enter other red blood cells. Not so in the mosquito. Within a period of from one to two days after this insect has bitten a person suffering with malarial fever the parasite becomes converted in some way into a kind of cyst

zygote or, according to some, an "oocyst," containing pigment, amorphous masses, and vacuoles. Within these same zygotes a few days later small thread-like filaments with thinned extremities develop and are arranged in rays around the central area. In the mosquito these bodies become the real spores of malarial fever. These spores or sporozoites require from three to ten days to develop in the middle intestine of the mosquito, after which time the sporozoon ruptures and pours out into the celom or body cavity myriads of these sporozoites, which find their way into the salivary glands of the insect, where they have been actually found to have almost blocked the lumen of the tubes which lead off from these glands.

Coming down to the manner in which these spores of malarial fever develop, MacCallum, Ross, Marchiafava, Bignami, Koch, and others hold to the belief that some of the crescentic parasites or the flagellated bodies which develop from them are of different sexes, thus conforming to the natural order of the Gymnosporidia.

Zoologically<sup>1</sup> the mature sexual forms of all micro-organismal life may be covered by the term "gamete," the female elements being known as macrogametes; the cells producing male elements are called microgametocytes, and the male elements themselves become the microgametes. Corresponding with this nomenclature, the free flagellum becomes the microgamete. Starting with the detached flagellum, it is known that it enters and fertilizes the female element or macrogamete, which, though it did not previously have flagella, now develops them rapidly, and has the power of penetrating dense tissues, such as the muscular layers of the middle intestine of the mosquito. This same process occurs in both the malarial fever of man and in bird malaria—proteosoma Labbé.

Having attached itself in this manner, the fertilized macrogamete becomes converted into the zygote—specimens of which have been loaned by Dr. Ross, which I have attempted to describe as follows :

*Examination with a Low-power Lens.* Examining the specimen with a No. 3 ocular and No. 3 objective lens (Leitz) with the dia-

<sup>1</sup> Twentieth Century Practice of Medicine, 1900, vol. xix. (Marchiafava and Bignami).



phragm well open one might at first sight be disposed to overlook any alteration from the normal appearance of the middle intestine, or, as some call it, the "stomach." The general appearance of the middle intestine of this insect is brownish and uniformly granular. If a portion of the light now be cut off and a proper shading be obtained one can see dozens of small round and dark granular-looking cells scattered almost uniformly over the entire area of the specimen. These cells have a uniform appearance, and may be picked out quite readily, even with a low-power lens. If one area be infected with the zygotes more than another, it may be said that the lower portion of the middle intestine contains the most of them. It is hard to count the number of these small dark areas, but I succeeded in counting over one hundred and fifty of them. Even with a low-power lens they could not be mistaken for the normal cells met with in the organ obtained from this insect. I have dissected dozens of specimens, and there can be no mistake about these cells being abnormal products. There might be some doubt about the identity of these cells were there only one or two of them, but in this specimen there are at least dozens of them.

With a low-power lens one may frequently see the broken spiracles or breathing tubes still attached to the middle intestine, as well as foreign pigment and large fat globules.

The minute structure of the zygotes (coccidia, oocysts, or sporozoons) must be studied with a  $\frac{1}{12}$  oil-immersion lens.

*Examination with  $\frac{1}{12}$  Oil-immersion Lens No. 3 oc. (Leitz).* On examining the specimen with a  $\frac{1}{12}$  oil-immersion and No. 3 oc. (Leitz), that which strikes the eye at once is the appearance of certain round, very prominent, yellowish or hyaline glistening, granular cells, containing a few minute granules of reddish pigment. All of these cells have a distinct capsule. At this stage (which are several days old) the cells range from probably fifteen to thirty microns in size. This is one of the peculiarities of the zygote, that they do not all develop at the same rapidity, and hence they are of different sizes. These cells or zygotes lie between the muscular fibers, which they displace to either side of the capsule. As a rule they seem to lie immediately upon the deeper epithelial cells of the middle intestine. Sometimes they

may protrude from the edges of the intestine, looking like excrescences.

A marked feature of these cells is that they are easy to find and not pale and indistinct, as are the other structures of the organ in which they lie encapsulated. In many respects they look like the type of malarial parasite from which they are derived. Ordinarily there are from two to seven or eight in each field in this specimen, which, however, contains an unusually large number of them. Examining the zygotes more closely, one observes that the cells have a more or less roundish or ovoid shape, with a thick yellowish glistening or hyaline capsule, in which lie scattered a few particles of garnet or reddish pigment granules, as well as a few glistening oval-shaped scattered masses of fat (?). The protoplasm has the faintest pinkish tint and has a reticulated appearance, and in some areas has a few slit-like vacuoles.

The small fatty(?) masses within the zygote are of different sizes, shape, and number. Usually they are ovoid or round, and some of them contain a single pigment granule. Frequently these yellowish hyaline masses are arranged in a circular manner about the inner lining of the zygote. This inner lining of the capsule is not uniform in thickness, but in certain areas it appears to grow inward, giving its interior a thickened or irregular aspect.

The occurrence of from one to six or seven dark-reddish pigment granules (destroyed hemoglobin) within the zygote is one of its main characteristics, this pigment being the inert matter thrown out by the malarial parasite, during its transformation into the zygote or coccidium. In all respects it resembles the pigment found in the malarial parasite of the blood. The appearance of this pigment, therefore, serves in identifying the zygote as being a derivative of the malarial parasite. The pigment dots are not always visible, but are brought out more clearly by focusing up and down. Sometimes one of these dotlets of pigment may be found in or near the inner lining of the capsule, and again two or more may be found lying near the center of the coccidium, but, as a rule, the pigment dots are found lying around the periphery rather than toward the center of this body. In these specimens of zygotes of proteosoma the pigment dots are found both in the young and in the older or larger forms.

## II. *Malarial Parasite from a Case of Malarial Hemoglobinuria.*

The next specimen which I desire to present is one of more or less interest from the stand-point of *etiology*. As is very well known, there is considerable difference in opinion among writers as to the real cause of the condition known as hemoglobinuria or hematuria coming on during an attack of malarial fever, particularly if quinine has been given previously to the onset of this manifestation. Some attribute the onset of hemoglobinuria or hematuria to the administration of the quinine, while others hold to the belief that such is due to the disintegration of the hemoglobin caused by the activity of the malarial parasites which are found in the red blood-cells.

Hoping to learn more of the type of the parasite which caused this condition, I last year sent out over many sections of the South cover-slips, with the request that blood specimens and also the history of such cases be sent me. So far only one reply has been received, this one being from Dr. W. Shropshire, of Yoakum, Texas. Unfortunately the cover-slips were simply enclosed in an envelope, and they were broken into innumerable particles when received. The blood-spreads were quite lumpy and many foreign particles were present. I was able, however, to stain several of these pieces (the blood being taken before and after the paroxysm of fever) by different methods, such as the Romanowsky method, by eosin and methylene-blue and by carbol-thionin.

The history of this case is as follows:

The patient was a man, aged forty-five years, occupation farmer, living in Dewitt County, Texas, and near a rivulet which at certain seasons was subject to overflows. He was a native of Georgia; blonde type. He has resided at his present location since childhood.

*Previous History.* For five years past he had been well, but previous to that time he had occasionally suffered from recurrent hemorrhages from the urethra, which he described as being due to "a kidney trouble," but which his present medical attendant believed came from the bladder. Two weeks previous to the present illness he had suffered from an attack of malarial fever, with paroxysms occurring every day. For this attack he took a patent medicine, which doubtless contained 2 or 3 grains of amorphous quinin, some Fowler's solution, and carbonate of iron.

*History of Present Illness.* Developed about the third week of September (?), and three or four days previous to the time he was seen by Dr. Shropshire. The patient had taken a few small doses of quinin (in the "chill tonic") about twenty hours previous to the onset of hemoglobinuria or hematuria, and about 10 grains of quinin had been given the day previous to the development of this condition. Thirty-six hours before he had been seen by the attending physician the man stated that he had been taking some medicine (probably calomel) sent by another attending physician, after which he began to pass dark or bloody-looking urine. He was seen at 7 P.M., at which time the temperature was 105°, pulse 112, and he was delirious, becoming maniacal when disturbed. The urine was of an acid reaction, dark-red color, specific gravity 1004, contained a moderate amount of albumin, urates, epithelium, hyaline casts, and degenerated red blood-cells. At this time the paroxysm was probably at its height, being 105°. Blood specimens were taken and sent to the speaker, and were stained with eosin and methylene-blue, and with eosin, and showed a few intracorpuseular parasites, having a somewhat oval or almond shape, and in the center of which could be seen a lump of dark pigment. The jaundice at this time was most intense, the sclerotics being yellow, but not to such an extent as the skin. The onset of hemoglobinuria developed at noon on one day, and at 10 o'clock on the following day the urine had almost entirely lost its reddish hue. The jaundice developed suddenly all over the body, and gradually became of a lighter tint as the condition of the patient improved.

At 7 P.M. the man was given 15 grains of quinin hypodermatically. On the following day at 10 A.M. the temperature was 103°, pulse 94, the patient was rational, and was perspiring freely. At this time other specimens of blood were taken and sent to the speaker and stained by the Romanowsky method. In these specimens, which were greatly damaged, I found at least one small intracorpuseular pigmented parasite, around which may be seen a faint clear or shining rim.

It is evident, I believe, that the infection from which the man suffered was from the *estivo-autumnal malarial parasite*. Seven days after recovery he had another mild attack of malarial fever.

Further history of this case elicited the fact that this man and all the members of his family had been bitten by mosquitoes, as the doctor states "the whole community had been alive with them." One other member of the family had severe malarial paroxysms at the time, and others had suffered from the disease, and in the opinion of the speaker this man was inoculated with the spores of malarial fever obtained from some member of his family.

*November 8, 1900.*

### Aneurysm of Abdominal Aorta—Recent Endocarditis.

M. H. FUSSELL, M.D.

Mrs. J., aged seventy years, was admitted to my wards in St. Timothy's Hospital, Roxborough, October 5, 1900. Family history negative. She has had eleven children, seven of whom died in infancy. She was never confined to her bed with illness. During the last spring she had sharp pains in her back, much vertigo, palpitation and dyspnea on exertion, and seven weeks before admission a severe chill. One week before admission she had severe abdominal pain with distention, which was thought to be an attack of peritonitis. On examination the following conditions were found: Heart dulness extended to outside of anterior axillary line. At the aortic cartilage there was double murmur. The same double murmur was heard along the sternum and at apex. The diastolic murmur was loudest at the apex. Both murmurs could be heard in axilla and in the back. Lungs negative. Abdomen: The walls were soft, retracted, and flaccid. To the left of the median line, under the rectus muscle and on a level with the umbilicus, there was a mass the size of a lemon, but extending upward as a fusiform mass toward the xiphoid. The mass was painful, fixed, and pulsated markedly, the pulsations being expansile. A systolic murmur could be heard over the mass. In knee-chest posture the pulsation was just as violent as when the patient lay on the back.

Exertion of moving caused much cyanosis of lips. The urine was normal. Blood examination, 3,950,000 red corpuscles, 14,000

whites. On November 7th the patient was seized with a convulsion which lasted one hour. This was soon followed by left-sided hemiplegia. The patient rapidly became unconscious. The left side remained limp, the right rigidly flexed. There was a slight rise of temperature each day, occasionally of septic type. She died comatose on November 9th. The leukocytosis was noted during the course of the septic temperature.

Postmortem five hours after death. Rigor mortis not present. A mass the size of an orange can be felt through the abdominal wall opposite the umbilicus. The lungs are emphysematous, otherwise normal. The heart is about normal in size; the left ventricle is tightly contracted. The left ventricular wall is thickened. The mitral leaflets are thickened, and the orifice admits only one finger. The anterior half of auriculoventricular orifice is converted into a stiff calcareous mass, which extends to the surface of the ventricular wall. The aortic leaflets are normal except one, which is thickened. Exactly in its middle is a recent granulation so long that it reaches the middle of the orifice. The tip is broken off.

The arch of the aorta is dilated and thin; the liver is small and granular; the left lobe has an extension which reaches far below the gall-bladder; the intestines are normal; the kidneys are somewhat granular. On removing the intestines the abdominal aorta is seen to be dilated just above the bifurcation. As a fact, the iliacs are found to branch from the dilatation in the aorta.

On dissecting the mass away from the spinal column, the posterior portion of the sac is found to be formed by the spinal column. The wall of the vessel has disappeared; the border of the vertebra is eroded; the sac is filled with a firm, fibrous clot.

It will be seen that wiring would have been useless, indeed impossible, in this case, as the vessel was already filled with clot. In all probability the diastolic murmur noted loudest at the apex was due to the mitral stenosis which existed. The observed leukocytosis was probably the result of the endocarditis. Unquestionably, the convulsion and the hemiplegia were embolic in origin.

*December 27, 1900.*

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### Parasitic Hemoptysis Due to *Paragonimus Westermanii*.<sup>1</sup>

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MR. PRESIDENT AND GENTLEMEN: It is with great pleasure that I respond to your kind invitation to discuss before you this evening the subject of parasitic hemoptysis, and to exhibit specimens of the parasite and the lesions it produces. My remarks will practically be an abstract of a paper<sup>2</sup> on the subject which will shortly appear in one of the publications of the U. S. Department of Agriculture.

A number of specimens of lung flukes taken from hogs in February have been forwarded to the Zoological Laboratory by Dr. A. J. Payne, Bureau of Animal Industry, inspector in charge at Cincinnati, Ohio.

As nearly as can be determined at present, the worm is specifically identical with the lung fluke known under the various

<sup>1</sup> Read by invitation, November 14, 1900.

<sup>2</sup> Ch. Wardell Stiles and Albert Hassall, Notes on Parasites, 51: The Lung Fluke (*Paragonimus Westermanii*) in Swine and Its Relation to Parasitic Hemoptysis in Man: XVI. Annual Report of the Bureau of Animal Industry (for 1899), 1900, pp. 560-611.

names of *Distoma pulmonale*, *D. Ringeri*, and *D. Westermanii*, for which Braun has recently erected a new genus *Paragonimus*. *Paragonimus Westermanii* (this being the correct binomial for the worm) was originally described by Kerbert, in 1878, from the lungs of a tiger which died in Amsterdam. A similar parasite was afterward found in man in Japan by Baelz and in Formosa by Ringer, and, though originally supposed to represent a new species, it is now generally admitted to be identical with Kerbert's form from the tiger. Ralliet (1890) afterward reported the same parasite from the dog in Japan, having examined some specimens in the Japanese department of the Paris Exposition of 1889; Ward (1894) reported it for the cat in the United States, and later (1895) he determined, as identical with this species, certain undetermined distomes which Kellicott (1894) had reported from a dog in Ohio. The present article is the first in which this lung fluke is recorded for hogs.

Referring to its systematic position, this parasite has always been placed in the family Fasciolidæ. Originally it was placed in the collective genus *Distoma*. Later it was transferred to *Mesogonimus*, which latter name was afterward suppressed in favor of *Clinostomum*. Blanchard (1891) recognized that the species in question was scarcely congeneric with the other members of the genus *Mesogonimus*, while Stiles and Hassall (1898) and MacCallum (1899) indicated its disagreement with the type species of *Clinostomum*, and intimated that this genus should be divided. Braun (1899) proposed for *D. Westermanii* the new genus *Paragonimus*, where it should now be placed.

The generic synonymy and diagnosis stand as follows:

Genus PARAGONIMUS Braun, 1899.

1899, December 11: *Paragonimus* BRAUN, 1899. Type, *Distoma Westermanii* Kerbert, 1878.

1899, December 30: *Polysarcus*<sup>1</sup> LOOSS, 1899. Type, *Distoma Westermanii* Kerbert, 1878.

GENERIC DIAGNOSIS. Fasciolidæ: Body medium large, thick, elongate, frequently oval, and on transverse section more or less round, usually somewhat

<sup>1</sup> Note: *Polysarcus* Fieb., 1853, orthopteron; *Polysarcus* Sauss., 1859, orthopteron; *Polysarcus* Lef., coleopteron; *Polysarca* Schin., 1866, dipteron.



attenuate toward posterior extremity. Cuticle provided with scale-like spines. Intestine with strong, somewhat elongate pharynx; very short esophagus; intestinal ceca zigzag, extending to caudal end of the body. Median excretory stem (or bladder), large dorsoventrally, irregular in outline, and extending cephalad to near the pharynx. Genital pore near caudal margin of ventral acetabulum, in median line or to the right or left. Copulatory organs (cirrus) absent. Testicles<sup>1</sup> round (?) or branched in posterior half of body, one each side of median line and one slightly posterior to the other. Ovary somewhat branched, the branches being thick and short, and the organ located posterolateral of the ventral acetabulum, on the right side (right or left side) of the median line opposite to the main portion of the uterus. Receptaculum seminis absent; Laurer's canal present. Vitellaria enormously developed, extending from anterior to posterior end of the body and located (as seen in cross section) on the periphery, usually leaving a longitudinal free space both in the dorsal and ventral median field. The transverse vitelloducts pass cephalad of the testicles, but caudad of ovary and uterus. Uterus may be only slightly developed or may form a comparatively large-sized roset, more than half as broad as the body. It may be located entirely on one side (right or left) of median line or may extend both sides of median line, partially covering the ovary. Eggs rather large, about 80 to 118  $\mu$  long by 48 to 60  $\mu$  broad. Embryo develops after oviposition.

HABITAT. Encysted, usually two in each capsule, in lungs of mammals.

TYPE SPECIES. *Paragonimus Westermanii* (Kerbert, 1878).

Leuckart compared Kerbert's specimens of *Distoma Westermanii* from the tiger with specimens of *D. pulmonale* from man, and gave the positive assurance that they were specifically identical, an opinion in which Nakahama concurred. So far as we are aware no actual comparison of the Japanese specimens from the dog with specimens from man has yet been made by any zoologist. Likewise no actual comparison of any of the American specimens from the dog, cat, or hog has as yet been made with any Asiatic specimens from man, tiger, or dog; but neither Ward nor we have felt justified, so far as we could judge from descriptions, in maintaining that the American lung fluke is specifically distinct from the Asiatic worm.

Even if it should eventually be shown that the American specimens are distinct from the Asiatic, still, in case the form found in dogs in Japan is actually identical with the form found there in man, there is reason to assume that the species found in the dog by Kellicott will also be able to develop in man. That man may

<sup>1</sup> Cobbold's figure of *P. compactus*.

harbor the same parasite as cats and dogs is supported by the fact that this particular worm is reported in Japan both for man and dogs, as well as by the fact that certain feline and canine parasites are also parasitic in man (*Coccidium bigeminum*, *Ascaris*, *Dipylidium*).

PARAGONIMUS WESTERMANII (KERBERT, 1878), STILES AND HASSALL, 1900.

**SPECIFIC DIAGNOSIS.** *Paragonimus*: 8 to 16 mm. (after Kellicott, 15 to 20 mm.) long, 4 to 8 mm. broad, 2 to 5 mm. thick; plump, pinkish to reddish-brown (alive) or slate (preserved) in color; live specimens are depressed and with variable outline; preserved specimens often oval to elongate pyriform, transverse section round or nearly so, anterior end bluntly rounded, posterior end less blunt. Oral sucker 0.53 to nearly 0.75 mm. (Leuckart) or more (0.864 by 1.017 mm. or 1 to 1.4 mm.<sup>1</sup>—Ward); or 0.80 to 1.12 by 0.80 to 0.83 mm. (Stiles and Hassall); 0.78 (Kerbert) in diameter, terminal or subterminal in different specimens from the same lung. Ventral acetabulum (0.6 to at most 0.75 mm.—Leuckart; 0.78 mm.—Kerbert; 0.75 to 1.017 mm.—Ward; 0.88 to 1.2 by 0.86 to 1.44 mm.—Stiles and Hassall) very slightly larger than oral sucker; situated somewhat anterior to middle of the body, 2 to 4 mm. back of oral sucker. Cuticle provided with broad scale-like spines.<sup>2</sup> Genital pore, often indistinct, closed to the caudal margin of ventral acetabulum, may be in the median line or immediately to the right or left of it.<sup>3</sup> Pharynx elongate; esophagus very short, so that the bifurcation of the intestine is considerably anterior to the ventral acetabulum; intestinal ceca usually somewhat zigzag, some distance from each other, run irregularly to posterior extremity. *Male organs*: Cirrus and cirrus pouch absent; ductus ejaculatorius straight; testicles tubular, ramified, one slightly posterior to other, on each side of median line. *Female organs*: Ovary branched, lateral, right or left of median line, somewhat posterior to acetabulum and anteroventral of transverse vitelloduct; on the opposite side of median line, at about the same height, is situated a lobate shell-gland and a rather short, massed uterus; in some specimens the latter may spread across the median line and partially cover the ovary; folds of uterus extend ventrally of shell-gland; vitellogene glands marginal, highly developed, extending from anterior to posterior extremity, often leaving but a small portion of the dorsal and ventral median field uncovered; transverse vitelloducts dorsal; vitelline reservoir large; Laurer's canal present. Eggs oval, 80 to 100  $\mu$  long by 56  $\mu$  broad (Leuckart); 96 to 118  $\mu$  long by 48 to 53  $\mu$  broad (Ward); 68 to 96  $\mu$  long by 48 to 60  $\mu$  broad (S. and H.); yellow shell. Mira-

<sup>1</sup> Suckers distorted, measurements not exact.—WARD.

<sup>2</sup> Largest in middle of the body, after Leuckart, but largest on anterior portion, after Kerbert; smallest around mouth, after Stiles and Hassall.

<sup>3</sup> The character attributed to this species relative to the situation of the genital pore on the left of the lateral line would appear to be somewhat diagrammatic; we have found it median, right or left, in specimens from hogs, and Kerbert reports it median.

cidium ciliated, develops after eggs leave the host. Sporocyst, redia, cercaria, and intermediate host not known.

HOSTS. Royal tiger (*Felis tigris*); cat (*Felis domestica*); dog (*Canis familiaris*); hog (*Sus scrofa domestica*); man (*Homo sapiens*).

LIFE HISTORY. The complete life cycle of the lung fluke has not yet been experimentally demonstrated. According to our present knowledge, the egg does not develop until it leaves the host in the sputum.

*Segmentation.* Pending confirmation of the alleged early segmentation of the egg before it is laid (Kerbert) or in the sputum (Manson), or of its possible development to the miracidium stage in the tissues of its host (Kellicott), it is more natural for us to expect, especially in view of Leuckart's observations, that the normal course of events is for the egg to be laid in unsegmented stage and to be expectorated in that condition. This is certainly what occurs in the form found in hogs. As yet no literature is accessible giving an account of how the segmentation of this species takes place.

*Miracidium* (ciliated embryo). Thus far at least two observers (Manson, 1882, and Nakahama, 1883) have succeeded in raising the embryonic stage. Manson (1882) states that when the eggs are washed free from the sputum and kept in water at a temperature of 80° to 94° F. (26.7° to 34.4° C.) an embryo develops in about six weeks to two months. This miracidium is ciliated only on the posterior two-thirds of its body, the cilia "extending as far forward as the rounding in of the shoulders." Nakahama's paper is in Japanese, and we are unable to read it, but according to Leuckart (1889) Nakahama succeeded in showing that when the eggs which are expectorated in the sputum are subjected to a temperature of 30° C. (86° F.) for twenty-eight days the ciliated embryo is developed. This miracidium is oval in form and is provided with a small projection on its anterior extremity. According to Manson, if expressed from the eggshells a week or two after the cilia develop, the embryos live in water only a few minutes, but at a later stage, when the miracidium escapes from the egg by its own efforts, it may live much longer. Manson kept one alive over twenty-four hours. From certain experiments detailed in his

article, Manson concludes that upon expectoration from the lungs the eggs perish unless they are freed from the surrounding mucus and have access to water; if, however, water is supplied to them even in small amount, they preserve their vitality. Thus it would appear that in water freed from the mucus and exposed to a temperature of  $80^{\circ}$  to  $94^{\circ}$  F. ( $26.7^{\circ}$  to  $34.4^{\circ}$  C.) the ciliated embryo develops in from four to eight weeks, and that certain conditions, such as not being freed from mucus and probably a lower temperature, retard the development.

How long the eggs preserve their vitality in dried sputum or in dust does not appear to have been established. From a hygienic stand-point definite information on this point is important. Remaining in moist sputum for any length of time, corresponding to a part of Manson's experiments, would probably rarely occur in nature.

Beyond the miracidium stage nothing is positively demonstrated in the development of *Paragonimus Westermanii*. As Leuckart remarks, it would be contrary to all analogy to assume that this is the infecting stage for man and other animals. On the contrary, the presence of cilia indicates an aquatic life, and, so far as can be foreseen from analogy, the miracidium, after swimming around in water, will eventually attack some invertebrate (probably a mollusk) and will develop into a sporocyst; rediae and cercariae will probably be formed, much the same as are described for *Fasciola hepatica*, and either an encysted or free-swimming cercaria will in all probability be the stage in which the parasite will enter its final host (man, cat, tiger, dog, hog).

Whether it will immediately attack the lungs, as suggested by Baelz, or first some other organ and later wander to the lungs, as suggested by Leuckart (1889), is an open question. In this connection reference may be made to the finding of an agamic distome in hogs' muscles by Mr. Bullard, at Buffalo, N. Y. It cannot at present be considered impossible that Bullard's parasites represent a younger stage of the lung fluke, either accidentally or normally encysted in the muscular tissue.

SOURCE OF INFECTION. The discussion of the life history and the assumption that a cercaria forms the infecting stage bring up several views expressed in Japan. Throughout the Asiatic liter-

ature on the subject frequent references are made to the water-supply, and it is clear that our Eastern colleagues look upon this as the source of infection. This view has much in its favor, and cautious persons will do well to drink only boiled or filtered water, especially when in infected fluke areas. The following references by various writers will be of interest in this connection. Manson (1882) in referring to one of his patients (Heng) writes :

He says he never exercised discretion about the water he drank, especially when young; used to take it from the river, well, paddy field, or ditch—which-ever lay most convenient; and he says that nearly all North Formosans are similarly indiscreet.

As prophylactic measures, Kiyono, Suga, and Yamagata (1881) advise against eating "raw eggs, uncooked fish, mussels," etc. Dr. Inoui and Yamagiwa (1890) state that in Okayama, where they studied a number of cases, a species of snail belonging to the genus *Limnæus*, and known as "Nina," is very abundant. Although they examined large numbers of these mollusks, they did not find any cercariæ, rediæ, or embryos of the lung fluke. Similar negative results attended their dissection of small fish. The peasants eat both snails and fish, but usually cooked. The inhabitants of the villages say that chickens suffer from a cough similar to that noticed in this malady, and that they eat the sputa of persons suffering from lung-fluke disease. On this account Inoui and Yamagiwa examined both chickens and eggs anatomically and microscopically, but without finding any trace of infection. As a prophylactic measure, Yamagiwa in a later article (1892) also advises against eating raw meat.

That chickens eat human sputa is a well-known fact, but the possibility of their becoming infected with lung flukes through sputum from lung-fluke patients may safely be looked upon as excluded. It seems possible that the cough referred to may be connected with the chicken disease known as "gapes," caused by *Syngamus trachealis* in the windpipe; while it seems more than probable that hens' eggs have fallen under suspicion because of the occasional presence of a fluke which, to the casual observer, is not entirely unlike the lung fluke; it belongs to the species *Prosthogonimus ovatus* and has nothing to do with *Paragonimus Westermanii*. As for not eating raw meat, the advice is good on

general principles, but it does not at present appear that such food will come into consideration as a probable source of infection. That Bullard's agamic distome in the muscles of hogs is the infecting stage of *P. Westermanii* may be admitted as among the remote possibilities, but hardly more. Very little pork is eaten in Northern Japan, and, while eaten more in Southern Japan, it is not a common article of diet among the poorer classes. This fact, and also the fact that the parasite is so much more common in men than in women, rather detract still more from the probability of such a source of infection. Should the unexpected prove to be the case, and Bullard's encysted form actually represent the long-looked for stage of *P. Westermanii*, ordinary curing or cooking will undoubtedly prevent all danger of infection. Of all possible sources of infection thus far suggested, the water-supply and the mollusks would appear to be more natural carriers of the cercarian stage than anything else. The lion, cat, dog, hog, and man—all of the animals for which this lung fluke<sup>1</sup> has been reported—are in the habit of eating meat, but all of them also drink water.

Since *Paragonimus Westermanii* has now been found in so many cases in hogs in the United States, it would indeed be strange if man had entirely escaped infection. In fact it seems quite probable that cases of parasitic hemoptysis have actually occurred in man in this country, but have remained unrecognized. We would naturally expect the first cases to appear in rural districts, and since the country practitioner does not, as a rule, use the microscope in diagnosis, such cases would naturally be mistaken for tuberculosis.

From a practical stand-point, not only because the parasite has already been found in America, in three different species of domesticated animals, but also because some of our troops returning from Asia may further import this disease with them, it appears advisable to bring the chief features of the malady to the general attention of practitioners as soon as possible. This must be done through the government reports, medical societies, and medical journals, as the disease is not discussed in American works on practice.

<sup>1</sup> *Herpestes*, the host of *Paragonimus compactus*, and *Lutra*, the host of *P. rudis*, are also carnivorous.

## THE LUNG FLUKE IN MAN (*Homo sapiens*) AS CAUSE OF PARASITIC HEMOPTYSIS AND JACKSONIAN (CORTICAL) EPILEPSY.

NAME OF THE DISEASE. The disease now under discussion is known under the following names.

ENGLISH.—*Parasitical hemoptysis* Manson, 1880, and *The Lancet*, 1880, *Endemic hemoptysis* Manson, 1883; *Lung-fluke disease* (as vernacular term); Pulmonary distomatosis (in part).

GERMAN.—*Parasitäre Haemoptoe* Baelz, 1880; *Wurm-Haemoptoe* Leuckart, 1889; *Lungendistomen-Krankheit* Yamagiwa, 1892.

FRENCH.—*Hémoptysie parasitaire* Chédan, 1886; *Distomatose pulmonaire* Blanchard, 1895.

ITALIAN.—*Emottisi parassitica* Sonsino, 1884; *Emottisi cronica* Sonsino, 1896.

SPANISH.—*Hemoptysis parasitaria* Bonis & Cortezo, 1882.

LATIN.—*Gregarinosis pulmonis* Bonis & Cortezo, 1882; *Distomatosis pulmonum*; *Gregarinosis pulmonum* Baelz, 1880.

The presence of lung flukes in man causes various symptoms, according to the location of the parasites. The two chief clinical forms in which the malady appears are the so-called parasitic hemoptysis and parasitic hemoptysis in connection with Jacksonian (cortical) epilepsy.

GEOGRAPHIC DISTRIBUTION OF THE DISEASE. Lung-fluke disease has been reported for the following places:

*Japan.* Hon-shu Island, from northeast (provinces of Awomori, Sendai, Izu, Shinano, and Gifu) to southwest (provinces of Okayama, Shimane, and Yamaguchi); also on the Kiushu Islands (provinces of Kumamoto, Nagasaki, and Kagoshima).

*China.* North Formosa especially, and Manson believes the large number of cases of hemoptysis he formerly noticed in central and southern Formosa are of the same nature.

*Korea.* Case of a Korean royal prince.

FREQUENCY. In a number of articles the statement is found that in certain parts of Formosa 15 per cent. of the inhabitants are affected. This statement is in at least one article attributed to physicians, but it appears to be due to an estimate made by a servant. Manson (1882) says, in referring to two Chinese patients:

Regarding their acquaintances, one of them said that 20 or 30 per cent, and the other that 15 per cent, spat blood. Possibly these are overestimates, but at all events they show that the disease is extremely prevalent.

Baelz, in a letter to Leuckart (1889), states that he knows of one village in Japan in which nearly all the inhabitants harbor lung worms. Taylor (1883) thinks it too early to make statements regarding the frequency of the malady, for the disease is usually mistaken for tuberculosis, since it can be diagnosed only with the aid of the microscope (not much used by Japanese physicians at that date), and since only a portion of the cases come to the notice of physicians. Blanchard (1895) states that in the provinces of Okayama and Kumamoto, both mountainous, the disease is so frequent in certain villages and so dreaded that the inhabitants of neighboring villages will have no relations with them, and even the physicians do not wish to go there because of fear of infection. (The origin of this statement has escaped us. See, however, Railliet, 1893.)

**PREDISPOSITION.** According to Yamagiwa (1892, p. 454), certain persons are more predisposed to the disease than others. From a helminthologic stand-point it may be questioned whether the fact that the disease has been found more in certain classes of patients than in others is due to an actual predisposition or whether it is not due rather to a greater risk of infection to which some persons may be subject. Thus tapeworms appear to be more common in women than in men; but this fact is due to women being more liable to infection (in preparing food) rather than to any constitutional predisposition. The various data gathered thus far are as follows:

*Age.* While the disease may attack persons of any age, it appears to be rarely diagnosed in very young or very old persons. From present statistics it is more common in persons in youth and early manhood. Thus of 59 cases compiled from literature, 45 were from patients between 11 and 30 years old.

*Sex.* Judging from statements by Eastern authors and from accessible statistics, the disease is more frequently diagnosed in male than in female patients, and it may therefore be assumed that men are more exposed to infection than women. Thus of



66 compiled cases of known sex, 58 were males and 8 were females.

*Occupation.* Taylor (1883) says that the parasite attacks persons irrespective of occupation. He is undoubtedly correct in this intimation that occupation is no protection against infection if the person is exposed. Yet there need be no surprise if, as is to be expected, persons following certain occupations will be more subject to infection than persons otherwise employed. From the few statistics thus far collected relative to occupation, it may be noted that of 51 patients 38 were farmers, 6 officials, 1 student, 1 laborer, 1 merchant, 1 coolie, 1 house boy, 1 shoemaker, 1 prince. Yamagiwa (1892) states that in Kumamoto students (hospital cases) are among the most frequently affected.

*Personal habits.* Yamagiwa (1892) records that 12 patients out of 38 were drinkers.

*Physical condition.* Several authors state that persons of strong constitution are more subject to the disease than persons of weak constitution.

**DURATION.** It is generally conceded that patients may live for years—ten to twenty, or perhaps more—after noticing the first symptoms.

**PROGNOSIS.** Patients may entirely recover if sent into a healthy noninfected area. Yamagiwa has repeatedly noticed cases of this kind where egg cysts were found in the mesentery, mediastinum, or lungs, but no adult worm was found. In general the prognosis depends upon (a) the number and (b) position of the parasites present, (c) age of patient, and (d) complications.

(a) The greater the number of parasites in the lungs the greater is the chance of severe pulmonary hemorrhage or of emboli in the brain.

(b) If the worms are confined to the lungs the patient may live for years. Severe hemorrhage or repeated profuse hemorrhages are naturally dangerous in proportion to the amount of blood lost within a given time. If the parasites or their eggs gain access to the brain, the prognosis is unfavorable.

(c) According to Yamagiwa (1892) development of patients under ten years of age is retarded by lung-worm infection, while in old patients the nourishment is considerably impaired.

(d) When complicated with pulmonary tuberculosis, prognosis is unfavorable.

DIAGNOSIS. Microscopic examination of sputa for *Paragonimus* eggs.

TREATMENT. Manson (1882) tried several treatments by inhalations, and thought they were not entirely unsuccessful. Taylor (1883) has no confidence in specific treatment, but advises a general course of medication, according to indication. Yamagiwa (1892) knows of no practical specific medical treatment. He thinks surgery might be tried if the exact position of the more superficial cysts could be more definitely located (X-rays?). By change to an uninfected region danger of reinfection is avoided and the parasites may disappear, becoming disintegrated, or, in some cases, possibly by being coughed up.

PROPHYLAXIS. Positive prophylactic measures cannot be given until the cercaria stage of the parasite is found. In general, however, care regarding the drinking water—to have it filtered or boiled—appears to be the most probable preventive measure which can now be proposed. There appear to be no valid grounds at present for suspecting eggs, fish, or meat, as suggested by some of our Japanese colleagues.

The following measures would undoubtedly accomplish much in preventing the disease from spreading:

(a) Infected patients should use sputum boxes, such as are used by consumptives. If cuspidors are used, it would be positively dangerous to empty their contents into any drain the sewage of which does not go directly into the sea. In all probability salt water would kill the miracidium. To empty cuspidors into a drain the sewage of which is used for fertilizing would be deliberately to comply with conditions which would be, on general principles, most favorable to the spread of the disease. If the sewage drains into a river the conditions for spreading the disease would also be very favorable. A comparison of the relative merits of the dry *versus* the wet cuspidor cannot be given until experiments in drying the eggs are conducted. On general principles the dry cuspidor would be better in this case (contrary to the conditions in tuberculosis), since, as a rule, trematode eggs are easily killed by drying.

(b) Cats and dogs which cough up blood should be examined for this parasite, and if *Paragonimus* eggs are found in the expectorations the animals should be killed and burned.

(c) If hogs are discovered coughing up a dirty yellow, brown, or bloody expectoration they should immediately be sent to slaughter. In abattoir inspection infected portions should be "tanked for fertilizer," but if healthy the meat of such a hog may be safely placed on the market. (See Abattoir Inspection.)

**SYMPTOMS.** The symptoms vary according to the location of the parasite.

(a) *Lung infection.* This is the usual form. Sputa very similar to that seen in pneumonia, and of a dirty red to brown color, due to the presence of microscopic worm eggs; spitting of blood common, but not constant, often intermittent; cough common, but not constant. All symptoms increased after violent exertion. *The only constant and specific characteristic is the presence of the eggs in the sputum; as many as 12,000 eggs may be expectorated daily.*

Manson (1882) gives the following as a typical case:

Heng, male, aged thirty-one years; resides in Singhang, Tamsui, where he works as a house coolie. His family, he says, is quite healthy; his mother, aged forty-four years, and three brothers and four sisters, are alive and well. His father died at fifty-eight years of dropsy, and a sister died in childhood of smallpox. He himself is liable to ague. He was born in the town of Banka and lived there till his eighteenth year; then he lived in Kelung for two or three years; afterward he removed to Hobe, Tamsui, where his home has been for the last ten years. He has travelled about the north part of the island a good deal; been in Tekchham two or three years ago, and eight months ago accompanied some Japanese to Khilai, on the east coast, where he resided for upward of a month. His blood-spitting dates from eleven years ago; he was then working on the tea hills with his father near Banka. At first he noticed, when he breathed hard in carrying heavy burdens, that he coughed a little and brought up mucus mixed with blood; but, as a rule, unless exerting himself violently, he brings up only a few drops mixed with the mucus. Sometimes he does not spit for a few days, and then the hemoptysis recurs, to last for one or two months. He has a slight cough, but on auscultation nothing much amiss can be detected. His thorax is finely developed.

Lung infection may be complicated by infection of the (b) brain, (c) liver, or (d) other organs.

(b) *Brain infection.* If the worms or their eggs gain access to

the brain, epileptiform attacks (Jacksonian or cortical epilepsy) may result. Cases have been reported by Otani (1887), Inoui and Yamagiwa (1889), and Yamagiwa (1890). The best accessible account of such cases is in Yamagiwa's (1890) paper. As causes of Jacksonian (cortical) epilepsy he gives:

- (1) Tumors of various nature—Charcot (1883), Obernier, and others.
- (2) Cerebral syphilis—Todd (1856), Charcot, and others.
- (3) Softening, cyst-building, sclerotic centers—Knecht, Fütterer, Hammond, and others.
- (4) Encephalitis, periencephalitis with adhesions, and meningitis—Huguenin, Burneville, Mendel, Sakaki (1889), and others.
- (5) Parasites, such as *Cysticercus cellulosæ*, reported by Griesinger (1872) and others; or *Echinococcus*, reported by Westphal (1873) and others; and *Distomum* (= *Paragonimus Westermanii*), reported in Japanese by Otani (1887) and Yamagiwa (1890). Since these and similar cases do not appear to have ever been published in English, it may be well to abstract one of them more or less in detail:

Otani's case was a twenty-six-year-old shoemaker, weakly since birth, but without any hereditary taint. In July, 1885, suffered from digestive troubles, with slight cough. Late in the spring—1886—he suddenly suffered from chills and fever, not malaria; had sharp pains in right thorax and severe attack of coughing. About a week later he noticed that his sputum was colored a dark-brown red. Ten days later felt much better, but bloody sputa continued; occasionally night-sweats, rise of temperature in the evening, and, in general, symptoms usually met with in consumptives. May, 1887, epileptic attacks began, one occurring nearly every month, but the intervals gradually increased in length.

September 9, 1887, admitted to the "inner station of the Kumamoto hospital." At that date temperature was 38.6° C. (101.5° F.); pulse rapid, weak, could hardly be counted; pupils contracted; "stands up and jumps as if he wanted to leave the bed." According to report, frequent epileptiform attacks had occurred since the evening previous. September 10, temperature, 37° C. (98.6° F.); pulse, 73; no attack, but patient very exhausted. September 12, again unconscious; temperature, 39° C. (102.2° F.); pulse, 100; more than ten attacks of cramps. September 15, semiconscious; temperature, 39° C. (102.2° F.); pulse, 120; keratitis of left eye; dirty-brown sputum, containing distome eggs. September 17, apathetic condition continues; temperature, 37° C. (98.6° F.); pulse, 80; a tightly adherent, hard tumor, painful to touch, size of goose egg, noticed in the fossa supraclavicularis. September 18, semiconsciousness continues; temperature, 38.8° C. (101.8° F.); pulse, 110. September 19, regained nearly normal consciousness. September 25, unconscious; temperature, 38.8° C. (101.8° F.); pulse, 106. September 26, death, with appearances of collapse.

(c) *Liver infection.* Two cases of cirrhosis of the liver with ascites have been observed. *Paragonimus* eggs were found in the interstitial tissue.

(d) *Infection of other organs.* Cysts of *Paragonimus* eggs in the mesentery, great omentum, etc., have not produced any notable symptoms.

**PATHOLOGY.** (a) *Lung infection.* On the surface of the lungs or directly under the pleura cysts are formed which are usually smooth. The cyst wall is composed of newly-formed tissue with round-cell infiltration and of loops of the bloodvessels in the surrounding tissue. These cysts may contain one, two, or several specimens of *Paragonimus* with their eggs, or only the eggs may be found. Charcot's crystals are always present, and occasionally cholesterin crystals.

Taylor (1883) summarizes the postmortem appearance as follows:

*Morbid anatomy.* Four postmortems have been reported—two in Okayama in 1881, one in Tokyo in 1882, and again one in Okayama in 1883. Others may have been made and reported, but they have not come under my observation.

Externally the lung presents little or no change in appearance. The parasites are found in the smaller bronchi, and also burrowing in the lung tissue. Whether the parasites in the bronchi are found adhering to the mucous surface by their suckers is not stated. When the lung is cut across their burrows are laid open, and, though varying somewhat, these are generally about the size of a filbert. They frequently communicate with one another, and always with the smaller bronchi, sometimes by several openings. Some communicate directly with a bronchus, the lumen of this latter and the burrow forming one cavity, while the bronchus presents the appearance of having a sac-like dilatation on one side. Such cavities are probably formed by the exit from a burrow to the bronchus becoming enlarged, and, finally, the partition between adjacent burrows breaking down and forming one cavity. Each cavity is surrounded by a ring of irregular induration, extending much further into the parenchyma of the lung in some directions than in others. The adjacent bronchi are congested and more or less inflamed. So, also, the circumjacent lung tissue is congested. The cavities contain broken-down lung tissue, hematin, ova, and débris, or dead specimens of the parasite. In one case twenty distomata were found. The contents of these cavities mixed with the mucous secretion of the bronchi form the characteristic sputa. It is evident that the irritation of the parasite may at times so increase the bronchial secretion as to give rise to a large amount of expectoration; while exercise, especially when the patient is at his worst, aggravates the condition. Though the mortality

from the disease is not high, there is no difficulty in realizing the condition of "physiological misery" that must necessarily accompany lungs in the condition described.

As all special treatment must be prophylactic, the most important question in connection with the disease is that of the mode of ingress of the parasite. It seems established that food is the medium. The Japanese consume large quantities of fresh-water snails and clams. Since the larvæ of various species of distoma are harbored by mollusks, it is probable that the parasite under consideration is in its larval state to be found in some of the mollusca consumed by the Japanese. The larvæ of other trematodes are found occupying one particular species as their host, and almost exclusively confined to that species. Such a species may be restricted to well-defined geographic limits, and thus the restriction of any parasitic disease, such as endemic hemoptysis, to certain regions would be satisfactorily explained by the corresponding restriction to the same regions of the conditions essential to the development of the parasite. What the intermediate host is remains to be determined, and when this is accomplished prophylaxis will take a definite and certain direction.

How the expectoration is produced has been pointed out, but the cause of the hemorrhage, which is always arterial, is not quite so clear. It is probable, however, that the parasite attaches itself to the mucous surface of the bronchi by its suckers, and when it releases its hold a drop of blood oozes out and appears as a pellet of blood in the expectoration [?], the larger hemorrhages being caused by the rupture of some of the capillaries or smaller arteries. Professor Baelz explains the bleeding by the passage of the larvæ from the circulation to the bronchi.

Hemorrhage, however, appears to be rather accidental than essential. In some cases it does not occur, and in these the expectoration is smoky or rusty, even when large in quantity. When small pellets of blood appear in the sputa from the first, they may and often do increase, small bleedings of half a drachm or a few drachms occurring frequently during a long period. But it is only in exceptional cases that the hemorrhages become frequent and large. Ova are not found in the pellets of blood or in the blood ejected during the course of a larger hemorrhage, but in the discolored expectoration, either with or without the bloody pellets.

A marked peculiarity of the disease is the irregular periodicity seen in so many cases. The occasional appearance of pellets of blood has substantially been accounted for, and the increased expectoration may be caused by accumulated contents of the cavities being poured out into the bronchi. The coughing thus produced keeps up expectoration until the cavities are comparatively empty, when the patient begins to convalesce. The fact that keeping quiet adds so much to the comfort of the patient at these times gives countenance to this hypothesis. But what becomes of the parasites themselves? Are they partially cast off in the abundant expectoration? One of my patients informed me that he had coughed up a worm. It was shown him under a low

power by the doctors in a native hospital, and from his description it probably was a distoma. I cannot, however, be certain, as I did not myself see the specimen. It is probable that some of the parasites may be got rid of in this way; but how long does each individual distoma live in the lungs? and is an acute attack an indication that a re-enforcement of the parasites has secured entrance? These are questions which I cannot answer. Many cases are known to have been troubled with bloody expectoration for as many as ten years, and in one the condition had lasted for twenty. It is not at all likely that the individual life of a parasite will cover these extended periods, nor is it necessary that it should. Living under the same conditions renders the patient liable to again and again receive into his person this insidious intruder. Nor can it yet be said whether a change of locality to a place where the disease is not known is attended with permanent advantage. Persons thus afflicted seem to have derived at least temporary benefit after a change of locality. Whether those affected with endemic hemoptysis are more liable to other pulmonary diseases is not yet determined. The probabilities are that a lung thus affected would be more vulnerable than a normal lung.

. . . To what extent the disease occurs in Korea is not yet known. It may yet be found in some parts of China. Two of the patients seen at the mission dispensary in Hiogo were Chinese residing in Kobé, but whether they had contracted the disease in Kobé or in China could not be satisfactorily ascertained, but most probably while in Kobé.

(b) *Brain infection.* Cysts with the parasite and eggs or the eggs alone, causing emboli, may be found in the brain. The first case was reported by Otani (1887), the second by Miura (1889), and the third by Inoui and Yamagiwa in Japanese in 1889, and later (1890) by Yamagiwa in German.

The chief lesions found on postmortem examination were located in the brain and in the lungs.

*BRAIN. Gross appearance.* The surface of the hemispheres did not show any material change. Several adhesions between pia mater and the right hemisphere, notably in the occipitolateral region; here the gray substance was somewhat harder than usual. Upon sagittal sections of this portion there were seen dark-gray points, surrounded with a white border and thus sharply differentiated from the remaining tissue; line of demarcation between gray and white matter indistinct. These structures were found chiefly in the occipital and parietal lobes and in the median portion of the central convolution, and were confined almost entirely to the cortical layer.

*Microscopic appearance.* The enlarged and thickened bloodvessels of the sulci are considerably ramified; the branches which extend into the gray substance are in part open, in part obliterated. If an obliterated branch is followed into the deeper portion of the gray substance there is found an irregularly shaped focus, infiltrated peripherally with numerous round cells, and

containing numerous brown bodies, the latter representing trematode eggs; in many cases the lumina of the smaller bloodvessels are filled with the same eggs. The surrounding proliferating and highly vascular connective tissue is infiltrated with round cells; also giant cells, occasionally containing eggs; further, also, in surrounding tissue are found numerous multinuclear Deiter's cells.

Yamagiwa then concluded that the primary location of the parasite which produced the eggs causing these egg emboli in the brain was in the lungs.

**LUNGS.** *Gross lesions.* On the upper left lobe were found here and there nodules of different size, with soft centers. The connective tissue capsule, which was highly pigmented and vascular, made them feel hard to the touch.

*Microscopic appearance.* The adult parasites were not found either in the lungs or in the brain, but the lung tubercles contained similar eggs and also giant cells.

It is interesting to note that the measurements of the eggs in the brain (40.3 by 24.5  $\mu$  to 64 by 40.6  $\mu$ ) were on an average (52.1 by 32.5  $\mu$ ) somewhat smaller than the actual (49 by 29.7  $\mu$  to 60.1 by 36  $\mu$ ) or the average (55.9 by 33.4  $\mu$ ) measurements of the eggs in the lungs. These variations Yamagiwa attributed to secondary conditions (direction of the section, compression, preservation, calcification, etc.).

Thus, to summarize, Yamagiwa shows: Disseminated circumscribed foci of trematode eggs, usually also with giant cells, in the cortical substance of the brain; localized in the occipital, parietal, and central lobes; surrounded by connective tissue new-formation and round-cell infiltration; thickening of the wall of the bloodvessels, especially of the adventitia, and obliteration of some of the branches; associated with lesions in the lungs containing eggs of the same species and giant cells.

(c) *Liver infection.* Cirrhosis of the liver resulting from emboli of eggs in the portal area (or perhaps coexistence of *Paragonimus* egg emboli with cirrhosis of the liver due to other causes).

(d) *Infection of other organs.* Cysts containing eggs of *Paragonimus* and fibrous nodules have been found in the mediastinum, diaphragm, mesentery, and walls of the intestines; and Otani is said to have found abscesses in the cervical and inguinal regions caused by trematodes. Eggs have also been found in the contents of the intestine. No lesions have been noticed in the spleen or the kidneys.

**ABATTOIR INSPECTION.** All lungs of hogs found to contain this worm should be "tanked" for fertilizer, in order to prevent dissemination of the eggs. There is, however, no danger of the



direct transmission of the worm from hogs to man, since analogy with other members of the same family (Fasciolidae) of parasites leads us to assume confidently that this species must pass through an invertebrate intermediate host (probably some mollusk) before it can infect another host. There is, therefore, not the slightest danger of infection from the eggs of the flukes connected with eating the pork from a hog which harbors the parasite in question, and inspectors should not, therefore, condemn the meat of such animals on the ground of the presence of the worms in the lungs.

In conclusion I should like to advance the fact of the presence of parasitic hemoptysis in this country as an argument in favor of the establishment of a Post-graduate School of Tropical Medicine. *Paragonimus Westermanii* is by no means the only exotic parasite which will be brought to this country, and our closer relations to certain tropical islands impose new duties upon our medical faculties in training men to practice in tropical climates. The discovery of this disease by American zoologists and veterinarians, who have thus been able to forewarn the physician to be on the lookout for the same malady in man, should also be recognized as a proof that zoology and human and comparative medicine are three very closely allied callings—a fact which, I regret to say, we in America are rather backward in acknowledging.

### Epithelioma of the Mouth and Skin of a Catfish.

JOSEPH MCFARLAND, M.D.

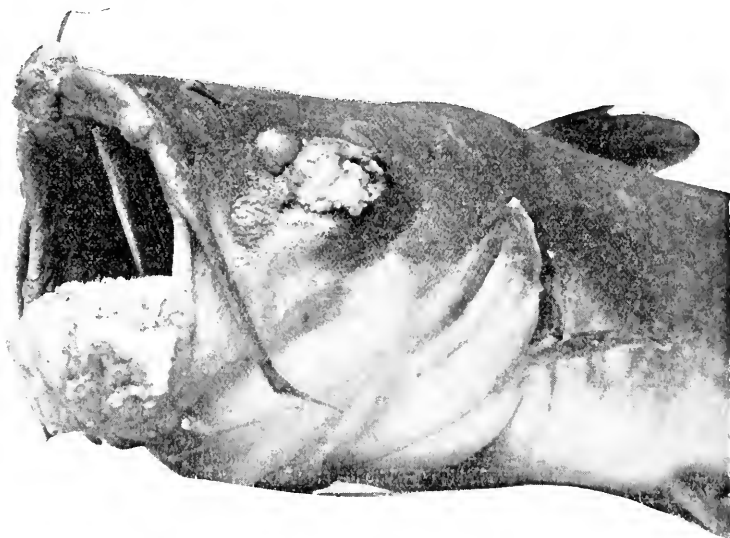
The specimen is a white catfish—*Ameiurus catus*, Linn.—which was brought to the Pathological Laboratory of the Medico-Chirurgical College by Dr. M. P. Dickeson, of Glen Riddle, Pa., to whom our thanks are due, both for the specimen as a valuable addition to our museum and for permission to describe it.

The fish measures thirteen inches in length. The left pectoral fin is of small size, evidently deformed as the result of injury. Except as further stated the animal is perfect.

What seems to be the primary tumor rises from the lower jaw,

apparently from the mucous membrane of the mouth, and forms a mass about  $1\frac{1}{2} \times 1 \times \frac{3}{4}$  inch, projects upward into the mouth and must have materially interfered with its closure. This tumor had an ulcerated surface and presented a distinctly lobulated and papillary appearance, the color being grayish-white.

Numerous nodules occur upon the head, six of them in a row along the edge of the upper jaw. Others were situated posteriorly and inferiorly to the left eye, over and behind the right eye, and upon the inferior surface of the neck. Most of the nodules appeared to be purely dermal.



There were no tumors upon the body, in the gills, or in the internal organs of the fish.

That the scattered nodules upon the skin of the head are secondary to that of the lower lip seems probable. The nodules along the upper lip suggest implantation.

The histologic study of the diseased tissue was made from fragments taken from the large node and from one of the growths upon the head. They show the neoplasm to be an epithelial growth—papillary epithelioma. It consists of a superficial fungous mass of branched papillæ composed largely of epithelial cells surrounding delicate fibrous and vascular outgrowths, and of a

deeper infiltrated portion made up of ingrowths of squamous epithelium forming large, rounded epithelial masses.

No epithelial pearls appear in any of the sections. The epithelial masses are extensively infiltrated with leukocytes, and in some areas an apparent edema and leukocytic infiltration have disorganized the epithelial masses so as to form soft and conglomerate tissue pulp.

The soft fungous character of the tumors and the absence of epithelial pearls lead me to believe that the growth originates from the mucous membrane of the mouth, not from the skin.

So far as I have been able to determine, this is the first time epithelioma has been observed in the fish. *January 10, 1901.*

### A Case of Hour-glass Contraction of the Stomach.

IDA E. RICHARDSON, M.D.,

AND

J. DUTTON STEELE, M.D.

*Clinical Report by Dr. Richardson.* The patient from whom the specimen was obtained was a white woman, thirty-eight years of age, and a native of the United States. Her grandfather died of tuberculosis of the lung. She herself was well and strong up to her fifteenth year; at that time she began to have symptoms of indigestion. There were periods of great pain directly after eating, which lasted for several weeks; this was followed by intervals of comparative comfort. Acid foods caused great distress, while sweet foods were well borne and appeared to give relief. For a time her diet consisted of bread, milk, and cream candy.

These symptoms lasted until the age of twenty-one years, when, under the effects of treatment, she greatly improved, until after six months the epigastric pain largely disappeared. About this time there was an attack of double pneumonia. In the course of a year, however, the pain reappeared and grew much more severe and at more frequent intervals. At the age of twenty-six years she had a profuse hemorrhage from her stomach. The blood was thick and black and came with vomiting. Some was passed from the rectum as well.

She then went to Southern California for some months, and came home much improved, with relief from the epigastric pain. After her return she was fairly well for six months, when the distress in her stomach began again.

In 1897, at the age of thirty-four, the pain became almost unbearable. As before, it was aggravated by eating, and there was much distention by gas, with eructation.

While in the West Philadelphia Hospital for Women, in 1897, her stomach was washed out after a test meal; the examinations of the contents gave a total acidity of 40; lactic acid, erythrodextrin, and zymogen were present. The examination of the urine showed nothing of importance. The pain was so great that tuberculous peritonitis was suspected.

At the age of thirty-two years she discharged a large quantity of pus from her lung, and after that she had a cough, some pain in the chest, and profuse purulent expectoration.

In 1897 a physical examination made while she was in the hospital showed symptoms of consolidation at the left apex, and tubercle bacilli were found in the sputum.

She died in 1899 at the age of thirty-eight years.

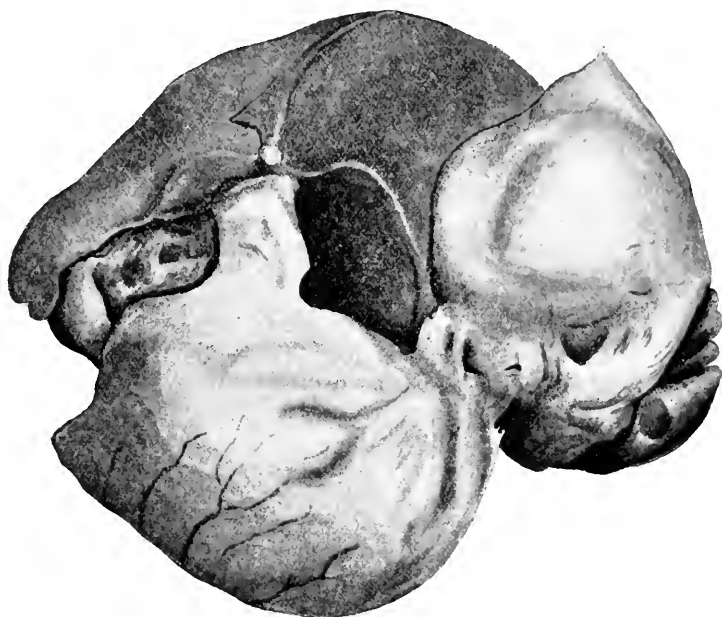
*Pathologic Report by Dr. Steele.* The notes of the autopsy are as follows :

The abdominal cavity was free from fluid. There were dense adhesions between the left lobe of the liver, which was very prominent, with what appeared to be the pyloric end of the stomach and with the head of the pancreas and transverse colon. The transverse colon was somewhat M-shaped and crossed a little below the umbilicus. The lower portion of the stomach was covered by coils of small intestine. When these were raised it was seen that the stomach was a typical hour-glass one, with the point of contraction at the point of adhesion to the pancreas and liver. The constriction just admitted the little finger to the first joint, which slipped by the ring of contraction with difficulty. The wall of the stomach in the upper half of the constricted area was thick, and the mucous membrane shining and scarred, and suggested scar formation. The capacity of the pyloric and cardiac divisions was about equal.

The pancreas was somewhat hard, but otherwise showed nothing of interest.

The hepatic flexure of the colon was adherent to the gall-bladder. The spleen was tightly adherent to the stomach.

The whole upper lobe of the left lung was the seat of an advanced miliary tuberculosis with numerous areas of softening. The middle lobe of the right lung contained a large cavity, evidently tuberculous. The bone marrow of the sternum was splenified. The heart showed some fatty degeneration of the myocardium.



Microscopic examination of the lungs showed them to be the seat of tuberculosis. The head of the pancreas and the area of the liver, bowel, and stomach so closely adherent were examined with especial reference to malignant disease. The adhesions were found to be fibrous in character and with no suggestion of any malignant process.

Examination of the stomach wall in the upper portion of the constriction showed that it consisted of a thin and distorted layer of epithelium much infiltrated by round cells, a rather firm layer

of fibrous tissue, the usual endothelial covering, and a very thin and distorted layer of muscle tissue. In places this last was entirely absent.

A piece of the stomach wall from near the pylorus showed some degeneration of the epithelium manifesting itself as granulation and vacuolization of the cells, and an infiltration of the epithelial layer with a considerable number of round cells.

The so-called hour-glass stomach is a somewhat rare condition. There have been four specimens of the condition presented before this Society. The first was shown in 1860 by Dr. Livezey (vol. ii, page 30). The constriction was apparently a result of contraction of a scar following an ulcer.

The second was reported by Dr. D. J. Milton Miller (vol. xvii, page 61). The stomach was constricted about its middle by secondary involvement of the stomach wall by a cancer rising in the head of the pancreas.

The third case was reported by Dr. A. E. Taylor (N. S., vol. i, page 183). The constriction was fibrous and its etiology uncertain.

The fourth case was one reported by myself at the first meeting of the present year. The constriction was of rather large caliber, and was apparently due to the healing of an ulcer.

In none of these cases was the condition diagnosed during life.

The constriction may be congenital, but it arises most frequently from the contraction of a scar, due to healing of one or more peptic ulcers; less often it may be produced by peritoneal adhesions or malignant disease. Riegel gives as the most usual cause the healing of ulcers that have involved both surfaces of the stomach and extend around the lesser curvature. The healing of several smaller ulcers lying near each other on the anterior and posterior wall may produce the same result.

The amount of constriction, of course, varies from the slight distortion of the shape of the stomach to the division of the viscus into two parts, connected by an opening that in some cases is extremely narrow. In the case here reported the communication barely admitted the tip of the little finger. In a case reported by Sache (*Virchow's Archiv.*, vol. cxxxiv) the opening measured about three-quarters of a centimeter in diameter.

As a rule, the two portions are not found to be equal in capacity at the autopsy, whatever they may have been originally. The cardiac segment is usually ectatic. This is caused by increased effort on the part of the stomach to force its contents through the narrow opening and to the consequent accumulation of food.

The symptoms are very indefinite and the condition is often not suspected until the autopsy. They are usually those of pyloric stenosis in the milder cases. In others the only evidences of the condition are those of the disease producing it.

The most characteristic physical signs are as follows :

First. A clear succussion splash over one portion of the stomach area, after the stomach has apparently been emptied by lavage.

Second. When the stomach tube has been passed and the washings are coming clear, there may be a sudden flow of gastric contents, especially when the stomach is massaged in the neighborhood of the pylorus. This sign is not absolutely trustworthy, as it sometimes occurs in cases of high-grade dilatation without constriction.

Third. Inflation with air through the tube shows the characteristic hour-glass shape of the organ. This, of course, is conclusive.

The microscopic examination in the case here reported, together with the macroscopic appearances, would indicate that the constriction was produced by the healing of an ulcer upon the lesser curvature about midway between the cardiac end and the pylorus, and involving the anterior and posterior walls. The history points rather definitely to the fact that the patient had suffered with gastric ulcer some twelve years previous to her death. The attack of hematemesis at that time probably marked the acute stage of the ulcer, which was followed by slow healing, and the beginning of the constriction. From that time onward the symptoms were those of dilatation of the stomach. The severe pain that led to suspicion of peritonitis may have been due to the extensive adhesions between the stomach, liver, and pancreas.

*January 10, 1901.*

## A Case of Deciduoma Malignum.

JOSEPH MCFARLAND, M.D.

The following case, although the true diagnosis was only recently made, was observed a number of years ago, and was reported in the *Medical News* for December 8, 1894, as a "Large Round-cell Sarcoma of the Uterus." The morbid specimens only are known to me, the case having occurred in the Kensington Hospital for Women, in charge of Dr. Charles P. Noble, to whom I am indebted for the following clinical memoranda:

Mrs. K., aged thirty years, white, married, mother of two children, the youngest of whom is thirty months old. Between the births of the children she had one miscarriage. In September, 1892, when the youngest child was about twenty-one months old, menstruation became profuse and continuous, so that by June, 1893, she was very feeble and anemic, and consulted Dr. Noble, complaining only of the hemorrhage. An examination was made and the uterus found to be much enlarged and discharging a foul-smelling bloody fluid. A clinical diagnosis of sloughing fibroid or cancer of the fundus was made, and on June 23d the organ was curetted and a large quantity of necrotic tissue removed. The amount of this material led Dr. Noble to believe that the case was one of sarcoma.

A fragment of the tissue was sent to me as pathologist of the hospital, and was subjected to microscopic study, with the result that nothing of interest could be determined, as the fragment consisted exclusively of necrotic tissue whose elements were no longer recognizable. I reported upon the findings and hazarded the opinion that the case was one of necrotic submucous fibroid.

The anxiety which Dr. Noble felt about the case led him to operate more radically without awaiting the result of my examination, and on June 28, 1893, a vaginal hysterectomy was performed. The patient made a good recovery from the operation, and remained well until November, 1893, then again called upon Dr. Noble, who found her ill in bed with profoundly embarrassed respiration, and aspirated about a pint of blood-stained serum from the chest, slightly relieving the symptoms. Several small



tumors were pointed out at this time, one under the skin of the breast, another under the skin of the loin, and a third under the skin of the thigh.

When seen later in her illness the patient was breathing 80 times per minute and the pulse was so rapid that it could scarcely be counted. The patient died December, 1893.

The extirpated uterus was sent to me for examination. It was enlarged to nearly the size of a small fist, the shape was pyriform, the surface smooth, the cervix normal. I opened the organ by a



longitudinal incision on the anterior surface and found a dark-colored, ragged tumor projecting into the cavity of the organ from the posterior superior wall. I did not receive the specimen in the fresh condition, but hardened in Müller's fluid, which prevents me from saying whether the tumor was originally soft or firm. The preservative had made it hard and firm, and the appearance was so completely suggestive of a submucous fibroid ulcerated and damaged by the curet, that I wrote to Dr. Noble that the microscopic examination confirmed my original diagnosis and that the

tumor was a necrotic fibroid. Some large sections of the tumor, extending entirely through it and through the uterine wall, were made, and a very careful examination made of the cervix. When these sections were examined I found the cervix normal, the uterine wall itself normal, but the supposed necrotic fibroid, consisting of a hemorrhagic and necrotic matrix, rather irregularly penetrated by areas of peculiar cells irregular in size and of very obscure histogenesis. I was much interested in this discovery, but failed at the time to determine its significance, and the specimens were laid away. After the death of the patient Dr. Noble wrote to me about her and the subsequent events in the course of the case, and I studied the sections again very carefully, and on December 8, 1894, published my opinions in the *Medical News*.

The case, therefore, has gone on record as a "Sarcoma (Endothelium?) of the Uterus." I doubt whether anyone would be able from the published description to determine that the case is one of deciduoma, though upon reading them over I find them so accurate that I need not repeat them.

The slides were again laid away for some years and might have remained untouched forever if in rearranging my collection I had not unexpectedly unearthed them. I remembered the peculiar tumor well, but had lost the mental picture of the histologic lesions. Upon again glancing over the slides the true nature of the growth, which in the meantime has become well known, became at once apparent, and I find it perfectly corresponding in detail to the numerous cases that have been published and figured since I wrote my original description six years ago. The microscopic appearances are well shown in the accompanying illustration.<sup>1</sup>

November, 1900.

<sup>1</sup> For the use of the cut I am indebted to the Philadelphia Medical Journal.

# Proceedings

of the

## Pathological Society of Philadelphia.

MARCH 1, 1901.

NEW SERIES, VOL. IV. NO. 5.

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### The Rapid Diagnosis of Rabies.

MAZÝCK P. RAVENEL, M.D.,

AND

D. J. MCCARTHY, M.D.

*From the Laboratory of the State Live-stock Sanitary Board of Pennsylvania and the William Pepper Clinical Laboratory (Phæbe A. Hearst Foundation).*

A rapid diagnosis of rabies is a matter of extreme importance for the physician and the patient as well as for the general public. There is perhaps no other disease which strikes so much terror to the mind of the average person, and the cry of "mad dog" is a signal for general excitement. Anyone bitten by a dog supposed to be rabid heretofore has been kept in a state of nervous suspense until it could be definitely determined whether or not the animal was a victim to hydrophobia. Up to the present time the only sure means of diagnosis in a vast majority of cases has been the inoculation of rabbits from a portion of the nervous system of the animal inflicting the bite—a practice often impossible to carry out with any degree of certainty on account of the poor condition in which such material is collected. Even under the most favorable circumstances from two to six weeks had to elapse before a positive diagnosis could be made. As well stated by Babès, it would seem "that this disease, so clearly characterized by a train of symptoms constant in their character, ought also to

present characteristic lesions in the nervous centers, and especially in the ganglia which preside over the production of symptoms," an opinion which has been generally accepted and acted upon by many students, their object being not only to disclose the cause of the striking symptoms, but also to find a method of diagnosis more rapid and more certain than any yet known.

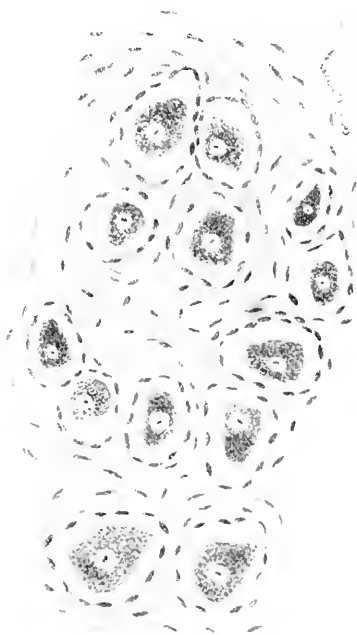
The first step in this direction seems to have been due to Polalion and Nepveu, who described the lesions observed in a man who had died of rabies. They noted that the whole cerebro-spinal axis was strongly congested, and that the ganglion of Gasser was hyperemic and infiltrated with round or oval cells, some of them being hyaline in appearance, and which they considered "probably epithelioid cells from the capsule of the ganglion cells." The work of Balzer, calling attention to the changes in the central nervous system, was followed in 1874 and 1875 by Benedikt's article, both authors describing the distention of vessels in the nervous centers, accompanied by an extravasation of erythrocytes and leukocytes into the perivascular spaces. Kolesnikoff, in 1875, described, besides, an invasion of the pericellular spaces by round cells occurring in the hemispheres, cerebellum, spinal cord, and the sympathetic and intervertebral ganglia. Schaffer also made a careful study of the vascular and cellular changes found in the case of a man, and called attention to a hyaline and fibrillar degeneration and vacuolation of the cells of the anterior horns of the cord. In 1886 Babès concluded, as a result of numerous researches made in man and in dogs, both natural and experimental cases, that the essential lesions of rabies consisted in an accumulation of embryonic cells in the neighborhood of the central canal, and especially about the large modified cells of the motor centers of the bulb and cord. Writing again in 1892 Babès reaffirmed his observations and insisted on the profound changes taking place in the nerve-cells. He held that it was possible to make a rapid diagnosis of the disease by a microscopic examination of the bulb and cord. He described in the bulb what he considered the diagnostic lesion of the disease, namely, the pericellular accumulations of embryonal cells described by Kolesnikoff, and for which he proposed the name "rabie tubercle." The cells of the bulbar nuclei undergo de-

generation and present the various stages of chromatolysis. There is loss of the prolongations and a progressive modification and even total disappearance of the nuclei, a dilatation of the pericellular space, and an invasion not only of this space but also of the nerve-cells by embryonal cells, and at the same time small corpuscles which are hyaline, brownish, and in parts metachromatic. Many of the nerve-cells become surrounded by a large zone of embryonal cells, and when the cell is completely degenerated these occupy the cell area and constitute the rabic tubercle.

Since 1891 Babès has examined the bulb of 487 dogs, controlling his results always by inoculation of rabbits. His results have led him to trust this means of diagnosis, and he still holds it to be one of the best means of rapid diagnosis at our disposal, although, except in Babès' own laboratory, the method does not seem to have been practised, at which he expresses a surprise which appears justifiable. Recently Nélis, working with Van Gehuchten, discovered in the spinal ganglia of two men who had died of rabies, and of a number of animals, peculiar changes which they considered to be the diagnostic lesion of the disease. They have confirmed all the lesions described by other authors, but in addition have noted what they consider to be more diagnostic than any other. The most profound, the most constant, and the earliest lesions are noted in the peripheral, cerebral, and sympathetic ganglia, and the changes are especially marked in the intervertebral ganglia and in the plexiform ganglia of the pneumogastric nerve. Normally, these ganglia are composed of a supporting tissue holding in its meshes the nerve-cells, each one of which is enclosed in an endothelial capsule (Fig. 1). The changes characteristic of rabies consist in the atrophy, the invasion, and the destruction of the nerve-cells brought about by new-formed cells derived from the capsule, which appear between the cell body and its endothelial capsule. These new-formed cells increase in number, invade the protoplasm of the nerve-cell, and finally completely occupy the entire capsule. These changes are widespread, but few capsules remain unaffected, and in advanced cases the section has very much the appearance of an alveolar sarcoma. The authors have considered in detail the findings of previous workers, but without exception they consider them as

secondary and without any importance, either in the production of symptoms or in making a diagnosis. They hold that Babès has attached an undue importance to his rabic tubercle. In their first publication they held that "these lesions are specific of the rabic infection, if not by their nature at least by their localization." In a later note, in answer to objections raised by Nocard and others, Van Gehuchten says that "the lesions of the cerebro-spinal and sympathetic ganglia which he and Nélis have discovered

FIG. 1.



Normal ganglion of dog. (Reproduced from Crocq, *Journ. de Neurologie*, v, No. 13.)

are not specific of rabies in general; they are only specific of the disease as it occurs naturally." It is to be noted that the authors have made no claim regarding an early diagnosis of rabies, but only a rapid method. Van Gehuchten says his method "concerns not a precocious diagnosis but only a rapid diagnosis in rabies." This has been further shown by the experiments of Cuillé and Vallée, who, after inoculating dogs with the virus of rabies, sacri-

ficed them at various times after the appearance of symptoms. They found that in animals in which the disease had just become manifested the lesions in the plexiform ganglion were slight or absent. They conclude that as a means of diagnosis the method of Van Gehuchten and Nélis has great value in the case of animals in which the disease has run its full course, ending in death.

The subject has been studied also by numerous veterinarians of note in Europe, notably Degive and Hébrant, of the State School at Cureghem, and Nocard and Vallée, of France, all of whom have obtained results confirming the value of the discovery. Quite recently Crocq has made a most thorough and complete review of the literature on the subject and a study of the method. He believes that Van Gehuchten is mistaken in considering the perivascular and pericellular neoformations described by Kolesnikoff and Babès as unimportant changes, and believes that by their constant character, their localization, and evolution they have a considerable diagnostic value. He says: "The lesions described by Babès and Van Gehuchten and Nélis are both remarkable. They are so great and so clearly defined that I can understand how the authors each on his side may have concluded that the alterations described by them were specific." The procedure of Van Gehuchten and Nélis is, however, more simple and rapid than the method of Babès, and on this account is to be preferred. Our own work leads us to believe that the changes in the intervertebral ganglia are more constant than those in the bulb, as will be seen by reference to the summary below.

The method of procedure recommended by Van Gehuchten and Nélis is as follows: The ganglion is put at once into absolute alcohol, in which it is left for twelve hours, the alcohol being changed once. It is then transferred for one hour to a mixture of absolute alcohol and chloroform; next put for one hour into pure chloroform; then for one hour in a mixture of chloroform and paraffin, and, lastly, in pure paraffin for one hour. The sections are put in the oven for a few minutes, then passed through xylol, absolute alcohol, and 90 per cent. alcohol, after which they are stained for five minutes in methylene-blue, according to Nissl's formula, differentiated in 90 per cent. alcohol, dehydrated in absolute alcohol, and cleared in essence of cajeput and xylol. If frozen sections are

cut they are put for a few minutes in 90 or 94 per cent. alcohol. In our work we have generally used 10 per cent. formalin for fixing our tissues. They are then transferred to 95 per cent. alcohol, and finally to absolute alcohol. For the most part the tissues have been cut without embedding, being attached to blocks by the aid of mucilage of gum-arabic, though in some cases celloidin has been used. For the bringing out of the chromatolytic changes the Nissl method has proved the best, but the capsular changes were best brought out in sections stained by hematoxylin and eosin. Since these latter changes are the most essential diagnostic features in the sections, we would suggest that material unfit for the Nissl method will still show the capsular changes when stained by hematoxylin and eosin.

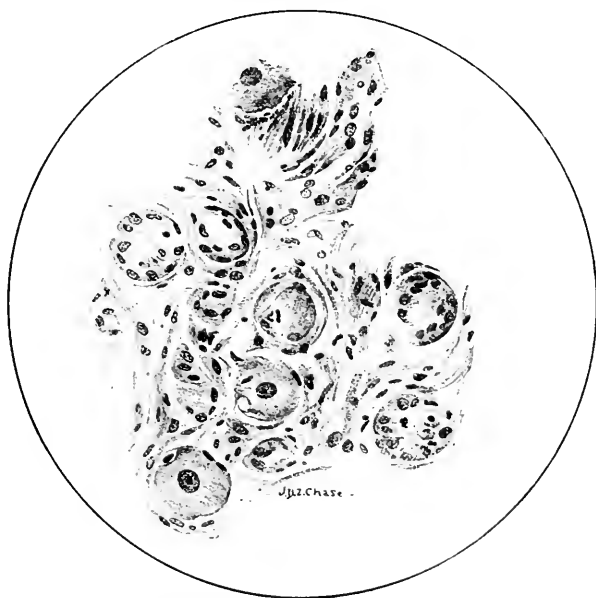
Up to the present time we have examined twenty-eight cases of rabies, including eleven dogs suffering with street rabies, one cow, one horse, and fifteen rabbits, which were inoculated from these animals, a few being of the second generation—*i. e.*, inoculated from the first experimental animal. In all of the cases studied (twenty-eight), except that of the horse suspected of rabies, we obtained positive results in the plexiform ganglia. In one case, however, the changes were slight and more marked in the peripheral (distal) portion of the ganglion. In twenty-one cases the bulb was examined for the rabic tubercle of Babès. Positive results were obtained in nineteen, though in two cases only chromatolysis, without distinct tubercle formation, was present. It will be seen that in two cases the rabic tubercle of Babès was not found, while the lesions described by Van Gehuchten and Nélis were present, though in one of these the changes in the ganglion were so slight as to leave us in some doubt. In this case, however, the subdural inoculation of rabbits gave positive results, and the microscopic examination of these rabbits showed the bulbar lesions of Babès as well as those of Van Gehuchten and Nélis in the ganglia. In the two cases mentioned in which the bulb showed only chromatolysis without distinct tubercle formation, the lesions in the ganglia were marked. One of these was the cow, which had shown clinical symptoms leading the veterinarian in attendance to suspect rabies. Two rabbits inoculated subdurally with the brain of this cow died with typical signs of rabies, and by



microscopic examination both the rabic tubercle of Babès and the lesions of Van Gehuchten and Nélis were found.

Of the rabbits examined three had been inoculated with virus of the second generation from dogs having street rabies. One of these rabbits showed symptoms of the disease on the eleventh day after inoculation, the shortest time which elapsed in any of our cases between inoculation and the appearance of rabiform symptoms. The microscopic examination of these rabbits gave positive results (Fig. 2).

FIG. 2.



Plexiform ganglion of rabbit dying of rabies produced by subdural inoculation. The capsules are filled or partly filled with foreign cells.

Of the dogs examined six had shown unmistakable clinical signs of rabies, while five were only strongly suspected of the disease. All the cases were controlled by the inoculation of rabbits except two dogs in which the clinical symptoms left no doubt as to the diagnosis.

In the summary of our cases we have not included one which occurred in a human being, for the reason that we obtained only a small portion of the upper cord, attached to which was a small

fragment of an intervertebral ganglion, not observed until sections were examined under the microscope. In some of the sections a few ganglion cells were found which showed the typical proliferation of the endothelial cells of the capsule. Rabbits inoculated with the cord gave positive results, and some of these have been included.

We take this opportunity of putting this case on record. The patient was a girl eight years of age, who came under the care of Dr. Frederick Krauss on August 12, 1900, by whom the diagnosis of rabies was made, and to whom we are indebted for the history. Six weeks before the child had been bitten on the right ear by a stray dog, which she was petting because it seemed to be sick. The dog was put out of the house and lost sight of. The wound was cauterized by nitrate of silver by a druggist, and healed without suppuration. On August 11th the child complained of lassitude, but was restless, and on account of these symptoms her mother gave her a dose of castor oil. The next morning inability to swallow was observed, being attributed to "sore throat," and soon after her mother noticed that on being touched with a wet towel or exposed to slight draughts of air she was frightened and startled. Dr. Krauss was called in on this day. The temperature was  $100^{\circ}$ ; pulse 120. On giving her a glass of water she would look at it with dilated pupils for a moment, then suddenly grasp it and quickly attempt to swallow a mouthful. Every trial was followed by severe tonic convulsive contraction of the pharyngeal constrictors and the more external muscles of the neck, lasting about fifteen seconds. Repeated attempts were made, always with the same result. In reply to a question she said that she was not afraid of the water, but it hurt her throat very much when she swallowed it. She shrank from the slightest current of air. Large doses of bromide of potassium and chloral with morphine were given, but without effect, and the symptoms grew more marked. She passed a sleepless night. On the morning of the 13th her temperature was  $101.5^{\circ}$ ; pulse rapid. Later in the day she developed a state of intense excitement. She would lie quiet and apparently conscious for a time; then, without warning, suddenly spring up to her mother, crouch down with short cries of fear, looking at the wall with an expression of great dread, and seem-

ingly unconscious of her surroundings. After about two minutes she would awake as from a dream. Repeated hypodermic injections of morphine had no effect, and she was sent to St. Christopher's Hospital. After a short remission the convulsive seizures became so frequent that almost constant inhalation of chloroform became necessary. When this was left off she would utter short and loud cries of fear, which might well have been mistaken for the bark of a dog, and attempt to spring out of the bed. Death took place on the morning of the 14th at 6 o'clock. The post-mortem examination revealed congestion of the brain and meninges and minute hemorrhages, while the severity of the convulsions was proven by rupture of the pleura. The train of symptoms left no doubt in the mind of the attending physician that the case was one of hydrophobia, and the diagnosis has been abundantly confirmed by the inoculation of rabbits, as well as by microscopic examination of the bulb and plexiform ganglia of these animals. The inoculations were carried through four generations, the rabbits all dying with typical symptoms of rabies, with the exception of one of the first generation, which died thirty-six hours after inoculation from septicemia. Besides the microscopic examination mentioned, full series of cultures were made, with the object of detecting any accidental infection during inoculation or after. These cultures remained sterile in every instance, so that we are able to exclude with certainty any known bacterial disease.

Our work has led us also to the study of a number of control cases which are as yet incomplete. So far as we have gone, however, they induce us to believe that the lesions described by Van Gehuchten and Nélis may for all practical purposes be regarded as specific of rabies. We bear in mind the opinion of Van Gehuchten himself, and held also by some other observers, that in dogs at least the changes in the cerebrospinal and sympathetic ganglia are only specific of the natural or street rabies. The lesions produced by the experimental inoculation of the "fixed" virus are not as marked as those in natural cases, and at times may be completely absent. We have not experimented with a fixed virus, but in rabbits inoculated with street virus of the first and second generations the gangliar changes have been marked. We have been convinced that the discovery of Van Gehuchten

and Nélis is of great importance from a scientific as well as a humanitarian stand-point. It can be rapidly and easily carried out, and should be a matter of routine in the examination of suspected cases of rabies in every laboratory.

In the examination of the medulla several sections were taken at random for mounting, but serial sections, extensive investigations of different portions of the bulb were not made, inasmuch as we were investigating rapid methods of diagnosis only, and not the essential nature nor the presence of these tubercles in the central nervous system. It is with this understanding that we recommend the examination of the ganglia rather than the bulb.

That these changes, or at least changes similar to them, might be expected in diseases where the intoxication is intense led us to inaugurate a series of experiments with tetanus and diphtheria toxins. In the meantime Crocq has reported his findings in the ganglia of a case of diphtheria, and since that time Spiller and Van Gehuchten have called attention to changes in three other cases resembling those found in the ganglia in rabies. In Crocq's case the proliferation of capsular cells was present, but the absence of the perivascular changes, which are as diagnostic as the capsular changes, made the differentiation comparatively easy. In Spiller's first case, endothelioma of the Gasserian ganglion, the presence of the tumor mass causing the irritation leading to the capsular changes, and the slow course of the disease, would lead to a correct conclusion. In the second case, one of meningo-myelitis, the resemblance is very striking, but the capsular, interstitial and pericellular changes are of such an intensity as is hardly met with even in the dog and horse, where the changes are much more intense than in man.

The attention which the subject has attracted, and the large number of investigations which are being made in consequence, will probably lead to the discovery of isolated cases here and there in which lesions closely resembling, or perhaps identical with, those under discussion will be found. So far only four such cases have been reported, all in man. While these are sufficient to make us doubt the absolute specificity of the lesion, it can be said with certainty that neither in man nor in any of the lower animals is there any condition known in which these changes

appear constantly, except rabies. Their occurrence in this disease is so constant and so marked that we cannot but believe that they have great diagnostic value.

From our study of this subject the following conclusions seem justified:

1. When present, the capsular and cellular changes in the intervertebral ganglia, taken in connection with the clinical manifestations, afford a rapid and trustworthy means of diagnosis of rabies.

2. That when these changes are not present it does not necessarily imply that rabies is not present. The lesions afford contributory evidence more or less valuable depending on the duration of the clinical manifestations.

3. That in certain cases when the capsular changes are slight, such as in animals dying or killed in the early stages of the disease, the changes are more marked in the distal-peripheral end of the ganglion.

4. That the rabic tubercle of Babès is present sufficiently often to furnish valuable assistance in cases where only the central nervous system is obtainable without any of the ganglia, but in cases where the ganglia can be had they offer a simpler and easier method of diagnosis than do the brain or cord themselves.

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#### Remarks on the Importance of the So-called Specific Lesions of Rabies.

WILLIAM G. SPILLER, M.D.

*From the William Pepper Clinical Laboratory (Phæbe A. Hearst Foundation)*

A study of the literature on rabies in connection with my examination of pathologic material from the nervous system has caused me to doubt whether the lesions described in cases of rabies could be considered as specific of this disease. It seemed to me exceedingly improbable that rabies could cause lesions so different from those of other diseases, and more probable that the proliferation of the cells of the capsules within the peripheral ganglia was merely a result of irritation or intoxication. In my examination of the Gasserian ganglion in a case of endothe-

hona of this ganglion, reported with Drs. Dercum and Keen<sup>1</sup> I found areas in which a proliferation of the endothelial cells of the capsule in the Gasserian ganglion, with complete destruction of the nerve-cell body, had occurred. These sections could not have been mistaken for those from cases of rabies, but they convinced me that from irritation, or intoxication, or some other cause, a tumor of this ganglion could produce a proliferation of the cells of the capsule about the nerve-cell body.

Another case from which I studied the brain and cord was sufficient to show that the lesions found in cases of rabies could occur in other diseases. This case was reported with Dr. Sherman<sup>2</sup> and was one of acute ascending paralysis (Landry's paralysis), and terminated fatally in thirty-eight hours after the appearance of the first definite symptoms of motor disturbance. The symptoms bore some resemblance to those of the paralytic form of rabies, as in the latter also the paralysis is ascending. I found intense inflammation of the central nervous system and pronounced perivascular cellular infiltration. In the lumbar cord, where the nerve-cell bodies of the anterior horns had nearly disappeared, were accumulations of cells in the positions normally occupied by nerve-cell bodies. It was difficult to say positively that these accumulations were always about the nerve-cell-bodies, as they concealed the latter if they were present. The condition was probably one called by Marinesco neuronophagia, to which attention has recently been called by de Buck and de Moor, and by Crocq,<sup>3</sup> *i. e.*, a destruction of nerve-cell bodies by round cells, probably derived from the neuroglia, and acting as phagocytes. I was able to find at least two nerve-cell bodies in one section from the lumbar cord, distinctly surrounded by round cells in the manner described by Babès as characteristic of rabies. The cellular infiltration of spinal ganglia from the lumbar region was intense, and in many places the proliferation of the endothelial cells of the capsules was distinct, and in some areas these endothelial cells have replaced the nerve-cell bodies. Small

<sup>1</sup> Dercum, Keen and Spiller, The Journal of the American Medical Association, April 28, 1900.

<sup>2</sup> Sherman and Spiller, The Philadelphia Medical Journal, March 31, 1900.

<sup>3</sup> de Buck and de Moor, Journal de Neurologie, March 14, 1900; Crocq, *ibidem*.

hemorrhages and perivascular cellular infiltration were also present in these ganglia. In this case, in which no suspicion of rabies ever existed, I found both the lesions described by Babès, and those described by Van Gehuchten and Nélis, and the lesions were more pronounced than in some cases of undoubted rabies. I, therefore, conclude that no lesions are specific to rabies, although under certain conditions the pathologic findings may be of considerable diagnostic importance.

#### DISCUSSION.

DR. RAVENEL said that he and Dr. McCarthy had realized from the beginning that the lesions described by Van Gehuchten and Nélis might occur in other conditions, but that so far they had been reported in only four cases outside of rabies. At present he was engaged in attempting to reproduce them in animals by tetanus and diphtheria toxins. Whenever the lesions had been found in the intervertebral ganglia and the plexiform ganglion of the pneumogastric there had been a definite train of symptoms, and from not a single case in which these lesions were present had he failed to reproduce rabies experimentally in the lower animals. Unquestionably the lesions had a diagnostic value, as had been illustrated in the cases of three persons who had recently been bitten by dogs. Within four days of the infliction of the bite and thirty-six hours after the death of the dogs Dr. McCarthy and himself were able to state that the animals causing the injury had been rabid. In the inoculated animals the incubation period was from sixteen to nineteen days. He believed that from a diagnostic stand-point the lesions in the ganglia would be of extreme importance and a real boon to humanity.

DR. MCCARTHY stated that in his opinion Dr. Spiller's sections did not entirely resemble those of rabies; they were much too intense, and did not show the irregular, individual ingrowth of capsule cells toward the center that had been noted in favorable sections from that disease. In the case of diphtheria reported in the literature (Crocq) the perivascular changes and the leukocytic infiltration of the cells were absent. He did not wish to say that the lesions described were characteristic; they might be found in

tetanus. Perhaps the most important point revealed by the studies on rabies was that this disease had a distinct, if not a specific, pathology, and that no one now who had studied it could doubt its existence.

In DR. SPILLER'S opinion, the intensity of the lesions could not be considered a strong point of differentiation, as it varied considerably in animals of the same kind affected with rabies. He asked Dr. Ravenel whether there were an ascending paralysis in animals other than rabies corresponding to Landry's palsy in man. A microscopic examination of the nervous tissues from an animal affected with such a paralysis would be important.

DR. RAVENEL, in reply to Dr. Spiller's question, stated that horses were subject to a disease called cerebrospinal meningitis, produced by ensilage, and asked that Dr. Ranck be called upon to answer the question.

DR. RANCK, in reply to Dr. Ravenel, stated that cerebrospinal meningitis, so called, or, as Dr. Pearson suggested, forage poisoning, might present itself as a very acute infection—the animals dying with symptoms of paraplegia—or, as was more usual, as a disease having a prolonged period of illness. He mentioned his experience in horses injected with the toxins of diphtheria and tetanus. In those receiving the diphtheria toxin, especially when the animals developed a high potent serum, a hyperesthesia manifested itself about the area of injection and eventually a general paralysis, under which the horses died. He suggested that it would be interesting to make a study of such horses, to determine whether there was the peculiarity in the nerve cells which seemed to be found in rabies.

*January 10, 1901.*

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### Pseudoporiasis Cerebri in Rabies.

D. J. MCCARTHY, M.D.

The occurrence of cysts of various kinds in the central nervous system has led to some confusion as to names. The most common cysts are those following hemorrhages, in which the clot is resorbed, leaving a cyst filled with a clear fluid. A cystic condition also follows, at times, thrombotic and embolic conditions in the



cortex. There is in some conditions of sclerosis a peculiar miliary cyst formation in the cortex, described by Marinesco and Serieux, and named by them cerebroporosis. A condition somewhat allied to this is found in those conditions of the cortex associated with marked wasting, such as parietic dementia, senile dementia, etc. This is the *état criblé* in which the pericellular and perivascular spaces are dilated, and other miliary cavities, probably due to the degeneration and disappearance of the ganglion cells, are present. The echinococcus cyst and cysticercus cellulosa also occur in the brain, and certain flukes have also been found in the brain substance.

The case I desire to report to the Society is that of a horse, the clinical history of which and the pathologic material I am indebted to Dr. M. P. Ravenel, of the Veterinary Department of the University of Pennsylvania. The horse was bit on the nose by a street dog sick of some disease, the nature of which was never determined, as it disappeared shortly after the horse was injured. About five weeks later the horse became ill; although previously docile and harmless, it became very vicious, and would bite the stall and attempt to grasp anything coming near it. It bit and badly lacerated its own body in several places, and exhibited toward the end marked delirium. Paralysis finally supervened, and the horse died. At the autopsy marked congestion of the central nervous system was noted on gross examination. Microscopic examination revealed the typical rabic tubercles of Babès. The perivascular round-cell infiltration of mononuclear cells was intense. The large ganglion cells were surrounded by small nuclei, probably proliferated glia cells; at times the cell had entirely disappeared, the small masses of glia nuclei and degenerated nucleolar pigment alone remaining. Inoculation into rabbits confirmed the diagnosis of rabies.

On gross examination sections through the pons and medulla revealed cavities ranging in size from that of a split pea to minute microscopic holes. They were scattered irregularly through the brain substance, and appeared to bear no relation to the bloodvessels. On microscopic examination these cavities were found to be perfectly circular in outline and were independent of any arrangement of the fiber elements or cell masses. There was no thicken-

ing of the glia, no round-cell infiltration, no inflammatory zone. In other words, they occurred in a brain showing the evidence of hydrophobia, but appeared to be independent of that disease. They were in all probability postmortem changes. The section stained with thionin, etc., revealed large numbers of bacilli scattered through the tissues and in greater numbers in the immediate neighborhood of the cavities. Exactly what air-forming bacilli this was it was impossible to determine from the morphology of the bacilli in the tissues. A case recently reported by Howard (*Journ. of Exp. Med.*, October, 1900), in which the lesions were similar to those in the present case, the bacillus mucosus capsulatus was found to be at fault.

Strong (*Journ. Bos. Soc. Med. Sci.*, 1899) gives the following classification of the air-forming capsulated bacilli:

1. Friedländer group, bacillus pneumoniæ Friedländer, bacillus ozenæ Fasching, bacillus sputigenes crassus, bacillus Wright and Mallory, and bacillus rhinoscleromatis (?). In these gas production is most abundant with saccharose, less with glucose, scanty or absent with lactose.

2. The aerogenous group—a rather wide group of bacteria in which gas formation is very abundant in glucose, lactose, and saccharose. To this group belongs the bacillus mucosus capsulatus, and it is not improbable that this was the micro-organism causing the cavities in our case.

Reuling and Herting (*Bull. Johns Hopkins Hosp.*, 1899, x) have reported a case of cavity formation due to *B. capsulatus aerogenes*. "Holes in the brain" were found in a case of universal cystic degeneration reported by Savage and White (*Trans. Path. Soc.*, London, 1883). This probably belongs to the class of cases here reported.

December 27, 1900.

### Cultivation of the *Aspergillus* on Urine.

L. NAPOLEON BOSTON, M.D.

The frequency with which one detects the presence of yeast and mycelium in the urine voided by the inmates of the Philadelphia Hospital prompted me to investigate the apparent relation existing between these and other fungi, which are in many respects similar.

For this purpose the *aspergillus fumigatus* and the *aspergillus niger* were cultivated on urine as follows: Acid, alkaline, and acid diabetic urines were placed in culture tubes, in quantities of 10 to 15 c.c. each. Where the urine was found to contain albumin it was heated sufficiently to precipitate this body, after which it was filtered and placed in tubes, as above stated. One-half of all the tubes were placed in a temperature of 212° F. for forty-five minutes. Tubes prepared in this manner were inoculated with the *A. fumigatus*, care being taken to introduce, as nearly as possible, the same quantity of the growth at each inoculation; always cultivating the organism on acid, alkaline, and acid diabetic urines. To accomplish this, six tubes, two of each variety—one of which was sterile—were employed. The same precautions were observed in the study of the *A. niger*. All inoculations were made April 13, 1900, and the following is a record of the changes observed; cultures examined daily to May 13, 1900.

*Series No. 1, A. Fumigatus.* Sterile acid urine kept at room temperature, four days after inoculation presented a surface growth which was easily broken by shaking the tube. Microscopic study detected clumps of mycelium. Many spores were found arranged in large clusters. Mycelial threads crossing one another were also observed. On the sixth day the urine was alkaline, of an amber color, and showed a heavy precipitate.

Acid urine (not sterilized) was rendered alkaline in four days—possibly due to bacteria. Growth less pronounced than on sterile urine. Microscopically this growth appeared to be composed of amorphous material and spores. Color amber.

Sterile alkaline urine presented a less pronounced growth than did acid urine. On the slightest agitation this growth sank to the bottom of the tube. (Alkalinity was increased on the sixth day.) The slight surface growth contained only few spores, while the color was slightly deepened. On the twenty-third day the surface and upper one-fourth of the urine were of a chocolate color, and by the thirtieth day this color had extended to the bottom of the tube. The sediment and surface growth at this time contained only few spores. To insure against the possibility of contamination, cultures were made from this tube, and were alike in giving negative results.

Alkaline urine (not sterilized) presented a more marked growth, which was found to be largely composed of spores. Alkalinity was not increased until the tenth day, when a browning was observed at the surface of the liquid, which increased gradually to the sixteenth day, when the entire urine was of a brownish-black color.

Sterile acid diabetic urine presented a whitish growth in forty-eight hours, covering the surface of the liquid; and on the fourth day tipping and shaking of the tube did not displace the urine, and the growth was beginning to acquire a greenish hue, while the urine remained of an amber color. Microscopic study detected many mycelial threads, each displaying its individual sporangium at one extremity, and few spores—the usual findings when the *A. fumigatus* is cultivated on potato or bread-paste. On the ninth day the growth was thickened, wrinkled and separated from the side of the tube, while its surface was studded with sporangia.

There was practically no difference in the reaction of the *A. fumigatus* when grown on unsterilized diabetic urine.

*Series No. 2, A. Niger.* Sterile acid urine showed a marked white surface growth on the fourth day, which prevented the urine from changing its position when the tube was inclined. This growth was composed of mycelial threads and many spores. Reaction neutral. Color unchanged.

Acid urine presented both a surface growth and a heavy sediment. The surface growth was composed of mycelial threads and spores. Reaction alkaline. Color unchanged. No further changes were observed.

Sterile alkaline urine presented but slight surface growth on the fourth day, and by the seventh day this growth had sunken to the bottom of the tube. This growth was found to be composed of granular material and few spores, which presented the usual dark color. Reaction neutral after the fourth day, and at the surface of the liquid a slight reddening was noticed, which increased to a deep cherry red.

Alkaline urine (not sterilized) differed only in that it was rendered highly alkaline, and at the thirtieth day the upper half of the liquid was changed to a dark brown.

Acid diabetic urine presented the same changes noted in the

study of the *A. fumigatus*, except that the culture medium required a dull black color, which was first observed at the surface and spread rapidly, discoloring the urine.

A review of the literature on aspergillosis, made by T. A. Rothwell, of Manchester, England, credits Rénon<sup>1</sup> as the first to call attention to the presence of mycelial threads and spores of this fungus in the urine of animals suffering from experimental aspergillosis (pseudotuberculosis). This author found that in from twenty-four to forty-eight hours after inoculation he was able to cultivate the *A. fumigatus* from the animal's urine, and in most instances he found mycelium—these findings being more constant as the disease progressed. At autopsy these animals were found to present classical lesions of the bladder and kidneys. Rénon attributed these findings to infection through the venous blood supply, as his attempts to cultivate the aspergillus on urine proved that it had little tendency to vegetate when kept at incubating temperature.

Many writers have called attention to the fact that the aspergillus and other fungi develop best on acid medium, at a low temperature; and the same has proved true in my study of the organism on urine, which probably explains the wide difference between the finding of Rénon and those of the writer. My review of the literature has been rather hastily accomplished, and possibly some records have escaped my notice; however, I have been unable to find any special record of the effect of this organism on human urine.

*January 10, 1901.*

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### A Case of Double Cortical Hemorrhage.

GEORGE W. NORKIS, A.B., M.D.

The patient was admitted to the Pennsylvania Hospital on Christmas day, having been picked up in the streets in an intoxicated condition. There was a slight lacerated wound of the left ear and temple. He was completely unconscious, had contractures of the left arm and leg, but no fracture of the skull. The next

<sup>1</sup> Comptes rendus des séances et mémoires de la société de biologie, Avril 18, 1896.

day he was sufficiently conscious to give his name, reply to a few questions, and was admitted to the ward of Dr. J. C. Wilson.

*Physical examination* showed an emaciated old man with sclerotic radial arteries, equal pupils, the eyes tending to rotate to the left while the head was drawn toward the right. Incontinence of urine and feces was present. Left facial palsy was noted, and continual irregular picking movements of the right arm and leg. The knee-jerks were absent on both sides, while sensation was unimpaired. Respirations were noisy and low pitched. A few days later the left-sided contractures gave way to flaccid palsy, and on the tenth day from the time of his admission the patient died. Examination of the urine had been negative.

*Autopsy.* No fracture of skull; no hemorrhage above the dura. Beneath this structure over an area corresponding to the middle of the right parietal lobe about a fluidounce of dark-clotted blood is seen. On lifting the brain from the skull more clotted blood is ejected from a softened area at the junction of the parietal and occipital lobes. The sulci of both these lobes are filled with blood.

At the termination of the Rolandic fissure a hemorrhage the size of a "quarter" is seen, which communicates with the central gray matter. On sectioning the parietal lobe the cut posterior to the Rolandic fissure shows a clot filling a softened area, one-half inch from the convex surface, about the size of a dime.

The cut posterior to this showed normal brain. The section posterior to this showed the hemorrhage first described (connected with the large subdural clot) to be distinctly isolated from the second smaller and more circumscribed one.

January 10, 1901.

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### Branchial Cysts and Fistulæ.

W. M. L. COPLIN, M.D.

As a result of the complex developmental processes requisite to the formation of the organs arising in the neck segment of the embryo a multitude of malformations is rendered possible. The formation of the branchial arches and associated clefts, or more properly furrows, and the fact that at the bottom of the furrows, internally as well as externally, the epithelium of the entoderm and ectoderm become contiguous, considered with possible errors at the anterior median junction of the projected developing columns, such as failure of median coalescence, it becomes at once apparent that all sorts of malformations or arrests in development may result. Such more or less complete persistence into extra-uterine life of conditions normally entirely fetal may be manifested by almost any degree of abnormality from fissure of the entire neck to trivial fistulæ, or from absence of more or less of the esophagus, lung, or other structure normally derived from the foregut, to the persistence of fistulæ (often of capillary dimension\*), blind sacs or cyst accumulations due to external and internal closure of canals without coalescence of intermediate tracts.

\* In one of Heusinger's<sup>1</sup> cases a thick whisker could be passed into the opening.

I shall not attempt to go into the developmental processes concerned in the formation of the branchial clefts, as such information is attainable in any of the current works on embryology.

Hunezowski<sup>2</sup> (1789) reported two cases of congenital cervical fistulæ; Dzondi<sup>3</sup> (1829) called them tracheal fistulæ, and Ascherson<sup>4</sup> demonstrated their pharyngeal connection. Heusinger<sup>1</sup> reported two cases and gave a table of forty-six cases. In his inaugural thesis (Paris, 1877) and later, Cusset<sup>5</sup> gives, with considerable detail, the result of his studies on the subject. Guzman's<sup>6</sup> thesis in 1886 and Bland Sutton's<sup>7</sup> work on tumors should also be consulted. Senn<sup>8</sup> discusses branchial cysts under teratomata. Recently Frederick Shimanck<sup>9</sup> reported cases of branchiogenic carcinoma, and reviews the literature of malignant disease arising in these abnormal cavities.

With regard to the classification of branchial cysts much diversity of opinion is found. Fevrier<sup>10</sup> speaks of median and lateral cysts. Depending upon their proximity to the surface the cysts are spoken of as superficial or deep. As it is not always possible to determine accurately from which cleft the cyst originated, the proposition to base the classification upon the embryologic origin of the defect can be scarcely regarded as satisfactory. Less satisfactory, probably, is the attempt to subdivide these cysts according to the contents, as the latter must be materially influenced by the presence of inflammation, hemorrhage, and infection, as well as its source; similarly situated and genetically identical cysts may contain dissimilar materials.

Based, however, upon the hypothesis that such a classification is justifiable, such cysts have been called atheromatous (branchial dermoids), mucous, serous, and hematocysts. As none of these cysts are primarily blood cysts, it is probable that the last-named subdivision is hardly justifiable. In Marsh's<sup>11</sup> cases the cyst contained a gelatinous material.

It has been proposed to name these cysts according to their anatomic position in the adult. From this point of view such cysts are called auricular or auditory, parotid, submaxillary, sublingual, pharyngeal, tracheal, etc. If carried to its legitimate conclusion such a classification would be scarcely consistent, as we would have substernal, sternocleidomastoid, and other anatomic subdi-



visions that would endanger our losing sight of the embryologic origin. Although possessing many disadvantages, the classification based upon the character of the cyst wall, taken in connection with the origin of the process, possesses many advantages. This would at once subdivide the entire group into two subgroups, one in which the wall showed to a varying degree the histologic characters of the skin and which would merit the name branchial dermoid, and the other in which the epithelial lining showed more or less striking resemblance to the mucosa lining the mouth, pharynx, or respiratory tract. Cysts of the latter type would be called mucous branchial cysts. While considering the subject of classification it is well to remember that the branchial cyst is but one type of a malformation that may be manifested by at least four pathologic possibilities. (1) Branchial fistulæ, canals extending from the external surface to one of the mucomembranous tubes or cavities, such as the pharynx, larynx, etc. (2) Where the external opening has been closed a blind fistula, pouch, or tract, with its internal opening retained, results. (3) An external fistula in which the pharyngeal, laryngeal, or other internal orifice has been closed while the external opening persists. (4) Cysts like that observed in the case reported in which both internal and external orifices have been obliterated, giving rise to a closed cavity the wall of which possesses an epithelial covering. In the experience of Trelat<sup>12</sup> fistulous openings are seven times as common as true cysts.

As already indicated, the structure of the wall depends to a certain extent upon the type of tissue that it imitates. In branchial cysts of the dermoid type the wall does not differ from that found in other dermoids except from the almost constant presence of lymphoid elements in the extradermal layer. This lymphoid layer may be scanty, consisting of a few aggregations of lymphoid cells scattered here and there, or such agminations of lymphoid tissue as to constitute distinct nodes. While it is true that other dermoids may occasionally possess more or less lymphoid tissue, it is very rare to find such accumulated masses as are observed in the dermoids of the type at present under consideration. In the branchial cysts imitating the mucous membrane in the character of the cyst wall the condition is practically always that observed

in the case here reported. In a small number of cases the lining has been composed of cylindric epithelium, rarely of the tall variety, and only exceptionally ciliated. Where the epithelium has been subjected to considerable internal pressure it may be flattened, of a low columnar (cuboidal) type, or less frequently quite resembling squamous epithelium. In only exceptional instances is it simple, usually stratified, the number of layers not uniform in different areas of the same cyst wall and not infrequently showing marked morphologic peculiarities in different areas of the same lining. When stratified the genetic layer shows more or less tendency toward a distinctly columnar type. It is not probable that epithelium is ever absent, and the only reported case that I have been able to find in which it was sought and not found is that recorded by G. Broesike;<sup>13</sup> but as the specimen was not studied in the fresh condition the absence of demonstrable epithelium is not surprising. The muscularis mucosa may be demonstrated with difficulty, or it may be, on the other hand, quite conspicuous. Sometimes it is composed of a scattered layer of smooth muscle cells, abundant at points, irregularly scant in other areas, and rarely arranged as a continuous membrane. Sometimes this layer is in immediate apposition, with a firm connective tissue stratum composed of fully formed fibrous tissue in which may be found numerous leukocytes usually of the lymphoid type. This fibrous tissue merges into the loose connective tissue by which the cyst is attached to neighboring structures. Elastic fibers are present in the case reported. Adjacent to the fibrous tissue, and when it is absent adjacent to the muscularis mucosa, could be found a varying amount of lymphoid tissue. Sometimes this lymphoid tissue is in type and arrangement a more or less accurate reproduction of the structure of the tonsil. In other instances there is a lawless aggregation of lymphoid elements, with a scant reticulum scattered along the submucosa at irregular intervals and in various sized aggregations.

A number of observers, Cusset,<sup>5</sup> Roth,<sup>14</sup> Monad and Dubar,<sup>15</sup> and Guzman,<sup>6</sup> have called attention to the presence of glands in the walls of branchial cysts. These glands may be of the serous or mucous type and show such aggregations as are found in the pharynx and esophagus of lower animals, and, though less abun-

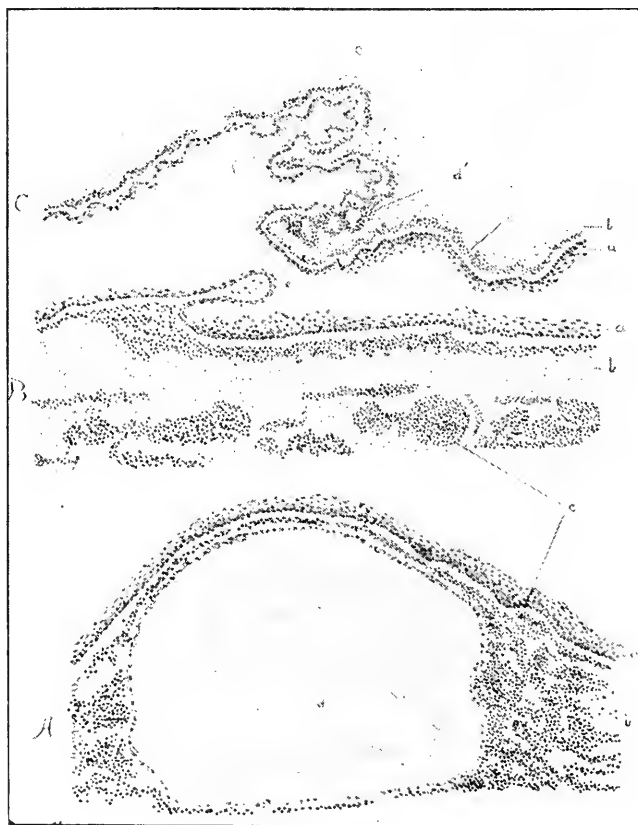
dant, in man; such glands may be distended by secretion, constituting true cysts in the primary cyst wall, or possess patulous ducts communicating with the general cyst cavity. Commonly the glands are not abundant, and apparently may be absent or overlooked. The cyst wall may be uniform and quite smooth, or it may be irregular, as in the case reported, of varying thickness, depending upon the amount of lymphoid and fibrous tissues rather than upon the thickness of the epithelial layers.

Sometimes the cyst extends in finger-like projections between the muscles, great vessels, and nerves of the neck, or behind the hyoid bone or downward behind the sternum or along the course of the auditory canal, rendering total ablation sometimes quite difficult, if not impossible. Sometimes the tumor projects into the pharynx or esophagus, or passes posteriorly to that structure or between the esophagus and trachea or larynx, and while presenting superficially as a rather simple and readily accessible mass, it may at operation present unexpected difficulties.

The communication of blind or open fistulæ with the air passages may give rise to air sacs; those sacs possessing internal openings into the trachea may present the features of that rare condition variously termed aerial goiter, aerial bronchocele, tracheocele, and hernia of the trachea. Stuart Eldridge<sup>16</sup> reported one such case and collected the literature bearing upon the subject. I gather from a perusal of his paper that he believed it quite possible for the defect to be latent, a mere point of weakness, which, under unusual stress, became manifest.

With regard to the symptoms of this condition little need be said, as they suggest themselves. The external opening of fistulous tracts may be situated almost anywhere in the anterior portion of the neck, about the auditory canals, in the temple, in the neighborhood of the jaws, etc., but always anterior to the sternocleidomastoid muscles. The external opening is commonly marked by a discoid area of scar tissue, or sometimes it may be so inconspicuous as to escape superficial examination. Only rarely can the fistulous tract be followed by a probe. Fevrier<sup>10</sup> reports the occurrence of severe reflex symptoms—pallor, palpitation of the heart—as a result of attempted exploration of a pharyngeal fistula. The discharge is usually clear mucus, but may be mistaken for

salivary secretion, from which it is easily differentiated by the usual chemical methods.



*A.* Section from thick portion of wall of branchial cyst. This section is richest in lymphoid tissue and shows the presence of the cyst *d*, containing granular detritus and lined by modified low columnar epithelium.

*B.* Section of wall of branchial cyst at point where thicker portion is thinning toward the extremely thin layer shown at *C*. Sections *A* and *B* are placed with the inner aspect of the cyst wall directed upward.

*C.* The section is reversed, the inner aspect being directed downward. *a, a, a.* Epithelial layer of cyst wall. *b, b, b.* Connective tissue layer. *c, c.* Lymphoid elements in cyst wall. At *d'* these lymphoid elements are aggregated in masses resembling the tonsil in structure. *e.* Section of one of the folds observed in the cyst wall. *f.* Irregularly dilated gland ducts. Tissue fixed in Heidenhain's solution, infiltrated with paraffin, stained with carmalum and picric acid. Zeiss 8 mm. Apoch. Projection eyepiece No. 2.

Where the fistula is complete and communicates with the esophagus or pharynx droplets of milk may escape during deglutition.<sup>7</sup> The location of the external opening is rarely a guide to the extent and relations of the fistulous tract or sac. Stimulation of salivary secretion by citric acid or mastication usually stimulates the secretion from the sinus even when it does not communicate with the alimentary canal.

When opening internally without an external opening the condition is commonly spoken of as a pouch or diverticulum (congenital);\* when communicating with the esophagus it may fill during feeding, or the internal opening may be so small as not to admit food. It may be evacuated by pressure, or the patient may find that by assuming a certain position the food does not enter the diverticulum.

Like the fistulæ the cysts are, in the neck, located anteriorly to the sternocleidomastoid, in the parotid or auricular region, in the neighborhood of the hyoid bone or maxilla, in the interclavicular notch, or less commonly substernal, presenting at the last-named point.

The character of the contents has already been considered. The striking resemblance in some cases to pus or to the caseous contents of tuberculous lesions may mislead the operator; as indicated in the report which follows, it would seem that the character of the cells found in the fluid should at once clear up the diagnosis.

With regard to the age at which the lesions manifest themselves, it may be said that the fistulæ are usually present at birth. They may appear later as a result of opening of pouches or cysts or incomplete extirpation. Like dermoids of other kinds the cysts may escape detection until adult life or later. In Cusset's<sup>5</sup> cases the patients were nineteen, fifteen, twenty-one, twenty-two, and twenty-six years of age. In the case reported the specimen was sent to the laboratory by Prof. W. W. Keen, to whom I am indebted for the following clinical notes:

"Mr. C. E., aged thirty-six years, first consulted me November 6, 1899, at the instance of Dr. C. W. Richardson, of Washington, D. C.

"His father and mother are living and in good health. Of his

\* For description of dissection see references Nos. 12, 13, and 16.

grandparents he knows nothing, except that his paternal grandmother died of old age at about eighty-five; he believes that all of his family were healthy. One sister died of diphtheria.

"Three years ago he noticed a lump on the lower jaw on the left side, no pain, no inflammation; in fact, no symptoms whatever. Its size was that of a peachstone until about eight months ago, when it began to grow quite rapidly. There have been, however, no symptoms connected with it, excepting a slight, dull pain about the side of his face, and he thinks it has affected his head in that he has become very forgetful. He has lost twenty-eight pounds in the last six months, weighing at present 175 pounds; but this may be due to other causes.

"On examination I found a soft, almost fluctuating tumor 10 by 6 cm., presenting the features of a lipoma.

"*Operation*, November 15th. An incision was made parallel with the jaw, and after cutting down through the mylohyoid the back of the tumor was reached. This proved not to be a fatty but a cystic tumor. The fluid looked very much like pus. My judgment was that it was a cold abscess either in the connective tissue or in a very much enlarged and softened gland. I was able to dissect the whole of it out, exposing at the bottom of the wound the great vessels of the neck. I very carefully washed the wound out with salt solution and then closed it with drainage. He made a perfect recovery."

### *Pathologic Report.*

*Specimen.* Cystic tumor of neck.

Specimen consists of an almost empty, flaccid sac measuring 7 cm. in its longest diameter. It is oval or slightly pear-shaped. It contains a pinkish-white, opaque fluid that resembles pus. The external wall of the cyst is covered by an arborescent outline of bloodvessels. The lines of dissection from the adjacent tissues are recognizable. By reason of perforations in its wall it was impossible to refill the cavity and determine its capacity.

Approximately one-half the cyst wall is thin (1 to 2 mm.), perfectly transparent, and containing a few bloodvessels. The remainder of the wall is thicker, but quite irregular in thickness. Its maximum thickness occurs in slightly bossed elevations ap-

proaching 1 cm. The average thickness of the wall does not exceed 0.25 cm. It is irregularly studded by grayish translucent elevations. The largest of these elevations are palpable, resembling tubercles. At one point in the thickened wall is a yellowish mass apparently caseous. This mass is ovoid, 0.7 cm. by 0.5 cm. in diameter. It is situated within the thickened wall and covered by a thin layer of tissue. At other points the cyst wall is traversed by thin septa dividing it into irregular depressions. In a general way the color is pinkish, with areas of what appears to be hemorrhage, some of which are purplish. At some points the wall is fibrous and very dense, in other areas it is soft and yielding. Weight 17 gms.

*Fluid contents of the cyst.* The quantity is insufficient to determine the specific gravity. The cells vary in size and contour, in the size of the nucleus, and in the quantity of perinuclear protoplasm. The best picture of these cells is obtained in spreads, dried by heat, and stained in hematoxylin and eosin, toluidin-blue and eosin, and Unna's polychrome methylene-blue.

1. The most abundant cell observed in such preparations is of relatively large structure, varying in size from 12 or 15  $\mu$  to 35 or 40  $\mu$ . In shape these cells are irregularly oval, a few are round or discoid, while by far the large part are irregularly polyhedral. The majority of these cells are mononuclear; occasionally a cell is to be found containing two nuclei, and in very rare instances three distinct nuclei can be recognized. Some of the nuclei, indeed, one may say the majority, are in a fair state of preservation. Nuclear fragmentation, fissuring, vacuolization and polychrome reactions are recognized. In some of the cells a distinct nuclear structure is no longer to be recognized. In others the nuclear remains are but faintly tinted, constituting irregular shadows in the cellular protoplasm, while in still others the chromatin is fragmented into irregularly outlined granules which stain unevenly. In many of the cells the nuclear margins are indistinct. The perinuclear protoplasm is for the most part finely granular and takes the acid stain with varying degrees of intensity. Its volume varies within wide limits; the different sized cells owe their differences in size to variations in the quantity of protoplasm rather than to any variation in size of the nucleus, which is rather

uniform. There are apparently free nuclei which probably belong to these cells, as indicated by the irregular, ragged rim of protoplasm which stains unevenly and often but slightly. The protoplasm is vacuolated in many of the cells, the vacuoles varying in size from 1 or 2  $\mu$  to 7 or 8  $\mu$ , clearly defined. In others the margin is ragged but sharply outlined, while in still others the protoplasm fades off and is gradually lost without any sharply outlined limit.

2. An occasional finely granular oxyphile leukocyte can be recognized, although the number of such cells is remarkably small.

3. Occasionally one finds a cell morphologically and tinctorially like a mononuclear leukocyte. These cells, however, are not abundant. There are a few masses of cells in which distinct differentiation cannot be made out, and within these might be included other cells than those described. A few erythrocytes are present.

A count of a thousand cells in spreads made from the fluid gives the following result in percentages:

1. The large cells resembling the squamous epithelial cells described above, 93.7 per cent.

2. Finely granular oxyphile leukocytes (polymorphonuclear leukocytes), 1.8 per cent.

3. Erythrocytes, 0.5 per cent.

4. Uninuclear leukocytes and unidentified cells, 4 per cent.

Portions of the cyst wall at various points were fixed in Heidenhain's solution, infiltrated with paraffin, sectioned, and sections stained with carmalum alone and with picric acid, hematoxylin alone and with eosin, Unna's acid orcein, Unna's polychrome methylene-blue, toluidin-blue alone and with eosin, toluidin-blue with differentiation in styron and glycerin-ether, and by Gram's method, and for tubercle bacilli with carbol-fuchsin.

For convenience in description, and for the sake of brevity, the sections from the following areas will be considered.

(A) Sections from the thin part of the wall. (B) Sections from the thicker areas.

(A) The best sections from this part of the wall are in the neighborhood of areas where the thin wall is suddenly or gradu-



ally converted into a thick wall by changes which will be mentioned later.

The inner aspect of the wall is lined by large polygonal cells evidently epithelial. Toward the free margin the cell outlines are not distinct; the nuclear stain is not strong, and vacuoles are abundant in the perinuclear protoplasm, which, under a very high power, is slightly granular; although it is impossible to give accurately the thickness of this layer (which varies) as it merges gradually with the cells below, it may be stated that it approximates two or three of the cell layers. Just under this layer the irregularly polygonal cells become more sharply defined both in outline and stain reaction. Toward the upper layer already described the nuclei are less distinct, becoming more and more clearly defined and stained with greater intensity as we approach the subepithelial layer. The germinal or basement layer of epithelium is irregularly columnar, with deeply stained nuclei, in some of which changes suggestive of karyokinesis are to be recognized. From this layer passing upward can be recognized the gradual transition from the irregularly columnar form to the more or less flattened, irregular and poorly stained cells already described as present upon the free surface.

As indicated by the above description, the epithelium of the wall cannot be divided into distinct layers, although there is the suggestion of a stratum corneum and stratum Malpighii. A distinct muscularis cannot be recognized in sections stained in the usual nuclear dyes, although here and there a few long, spindle-shaped cells with rod-like nuclei are to be recognized. In sections stained in acid orcein a delicate basement membrane can be recognized at nearly all points; this structure sends trabeculæ downward in many areas, penetrating the lymphoid tissues below. While the stratum germinativum is slightly irregular, one cannot say that there is anything more than a mere suggestion of papillæ. Immediately under the epithelial layer described one finds nearly the whole length of the section a slightly irregular layer of lymphoid tissue. The reticulum varies in quantity, being at some points rather abundant and at other areas scanty. It is not rich in bloodvessels, particularly toward the epithelial surface; as we approach the outer limits more vessels are to be recognized. The

cells occupying the reticular spaces correspond for the most part with the usual type of lymphoid cell, and scarcely merit further description. A few finely granular oxyphile leukocytes are present, although there is certainly no excess of these elements. At points the outer wall, or I might better say outer limit of the wall, is formed by lymphoid tissue. In other areas it is formed by masses of fibrillated connective tissue comparatively rich in blood-vessels and containing a few unstriped muscle fibers. The roughened and irregular free margin at this point is, of course, due to its dissection from adjacent tissue. I have not been able to demonstrate the presence of striped muscle fibers in this area.

(B) Sections from thicker areas in the wall. As the increased thickness of the wall in different areas is due to different causes it would be necessary to consider these areas separately.

1. Areas in which the thickening is due to a thicker wall of lymphoid tissue. The epithelial covering in these areas deserves no special description as it varies little if at all from the epithelial layer seen in the thinner wall. Partly as a result of its increased thickening, and possibly from other causes, the cellular elements usually present on the mucous surface can be more readily recognized, although as is usual under such circumstances differentiation into layers is not clear. Cross sections of flattened cells, such as those already described as present in the fluid contents of the cyst, with flattening, or slight elongation of their nuclei, are to be recognized. There is the same gradual transition from the irregularly columnar germinal layer to the flattened surface layer already described. In some of the thicker areas the lymphoid tissue is more abundant and the reticulum scanty. In other areas the reticulum is more abundant with a suggestion of proliferative change and corresponding reduction in the richness of lymphoid cells. Distinct arrangement of cells, such as composes adenoid follicles of a lymphatic gland can be recognized, and occasionally there is a suggestion of medullary cords, although demonstration of these structures is not complete. External to the lymphoid areas just described there is the same area of fibrillated tissue containing a few long spindle-shaped cells with rod-like nuclei. A further study of these lymphoid masses reveals the presence of necrotic spots. Such points embrace only a few cells. Just beneath the

germinal layer in some of the sections there is a lymphoid infiltration of the connective tissue not associated, however, with the presence of finely granular oxyphile leukocytes. These bodies are not abundant in any point in the section.

2. Areas in which the increased thickening of the wall is due to the presence of cysts. The epithelial covering in these areas merits no further consideration than that already given. Only one of these cysts will be described. In designating this distinctly as an additional cyst the possibility of its communicating at some point with the larger cysts cannot be overlooked, although such communication cannot be demonstrated even in serial sections. The wall of this cyst is formed by an inner zone of squamous epithelium which has been detached or has disappeared from some areas. It shows the same general appearance as that already given for the epithelial lining of the larger cyst. At one point the two cavities are separated by a thin wall less than 1 mm. in thickness, composed of two epithelial surfaces between which is a small quantity of fibrillated tissue rich at points in lymphoid cells.

Macroscopically on section this cyst possesses a diameter of 0.3 cm., and corresponds with what was mentioned in the gross description as a distinctly yellowish mass measuring 0.7 by 0.5 cm. The difference between the diameter in the gross specimen and the section is probably to be attributed to shrinking and the removal of fluid from the interior of the cyst, or to the section not passing through the greatest diameter. The cyst contents as examined in the fixed and infiltrated preparation are usually composed of fine, intensely acidophilic granules resembling in many respects the detritus in caseous areas. That it is not caseous in the true sense is shown by the fact that it contains large squamous epithelial cells, such as have been identified in the fluid from the larger cyst. Most of these cells have lost their characteristic stain reaction, selecting only the acid dye and, therefore, possessing indistinct, irregularly defined nuclei and cell outlines.

The contents as here studied must be considered to be the product of degenerative changes in the epithelium which has been cast off into the cyst cavity. Three smaller cysts identical in all their essentials with that just described have been found, and it

is reasonable to infer that the many small whitish or grayish, translucent elevations mentioned in the gross description were probably, or at least some of them, cysts resembling the one just described.

3. Sections from other areas in the cyst wall show evidences of chronic inflammation manifested by a lymphoid and plasma cell infiltration with the production of fibroblasts, and in some areas cicatricial tissue. At a few points the mucosa shows distinct papillæ. They are, however, not abundant. Occasionally there is a distinct fold resembling the irregularities or rugæ often observed in mucosa surrounding cavities whose walls possess considerable distensibility. Transverse section of the overhanging rugæ gives the appearance, at times, of superficial gland-like projections. Serial sections, however, show clearly that these are folds. In other areas distinct glands are demonstrable, and it is evident that the cysts already described have resulted from distention of gland acini, or ducts, or both.

*Bacteriology.* Cultures were not obtained from the cyst contents. Spreads and sections show the presence of a few cocci in the cyst contents and in the wall; these cocci stain by Gram's method, are apparently staphylococci, few in number, and the absence of cellular infiltration as well as the scant necrosis would indicate that the infection, if such existed at the time of extirpation, was inconsequential.

*Diagnosis and Remarks.* There can be no doubt of the branchial origin of this cyst. The character of the epithelial covering, its arrangement, the morphology of its cells, the structure of the submucosa, the presence of cysts in the wall, the abundant lymphoid tissue and the cyst contents all point to the branchial origin. From a practical view the character of the cells found in the fluid contained within the cyst offers important diagnostic aid. The small number of leukocytes of the type usually found in pus, and the presence of large mononuclear cells rich in perinuclear protoplasm, and the absence of necrotic material, should be in the future of value in diagnosis. In cysts of endothelial origin, similarly located, it is not likely that exfoliated cells would ever present the morphologic and tinctorial characters recognized in the case reported. Endothelial cysts possessing richly cellular

fluid contents would, no doubt, owe their cellular elements to the presence of migrated leukocytes and exfoliated endothelium, in which case no such cell count as that reported would be found. It would, therefore, appear to the writer that an examination of the fluid that came from such a cyst, taken in consideration with its location and clinical history, should make the diagnosis less difficult than it at first appears.\*

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*January 10, 1901.*

### Multiple Tumors of the Sciatic Nerve.

JOHN B. ROBERTS, M.D.

As tumors of the sciatic nerve are comparatively rare the following case is placed on record.

A man, aged 39 years, came under my care on January 22, 1901, with the statement that fourteen years ago he had first noticed three small tumors about the size of peas on the outside of the left leg near the knee. After an attempt had been made to

\* Since reading the foregoing paper the writer has had an opportunity to examine two branchiogenic specimens. One a squamous-cell epithelioma situated just under the lower maxilla midway between the median line and the anterior margin of the sternocleidomastoid. When the tumor first appeared it was movable, and it was thought to be an enlarged lymph gland. The second specimen was a typical branchial cyst with very thin walls, and so collapsed when delivered at the laboratory that it was quite impossible to accurately determine its size. Although the specimen was received immediately after removal a large portion of the wall was void of epithelium; the remainder was covered by irregular areas of tall columnar epithelium, which at points was ciliated. The lymphoid tissue in the wall was unusually scanty. The patient was a female, aged thirty years.

remove these with a caustic plaster, an incision was made, about six years ago, and three small tumors which were called fatty tumors were excised. The man said that for the last fourteen years he had suffered with pain in the left popliteal region.

About five years ago he observed that there was a lump to be felt deep in the left popliteal space. This tumor has been increasing in size and is painful on pressure. It is for this condition that he applies for treatment. The pain runs up and down the leg from the seat of the tumor, which is a spindle-shape mass apparently about an inch and a half in length. The tumor lies directly in the middle line and is plainly felt when the knee is flexed so as to relax the tissues of the ham. The pain is continuous and worse at intervals. It sometimes keeps him from walking, and he has been unable to work for about six years. He says that there is weakness in the left leg and numbness of the foot. He complains of sweating of the left foot. It is always warmer than the other and its stocking is frequently saturated with perspiration.

I requested the resident physician of the Methodist Hospital, Dr. Charles P. Stahr, who had immediate care of the patient for me, to refer the case for examination to Dr. James Hendrie Lloyd; but, unfortunately, Dr. Lloyd was not able to see the patient before the day fixed for operation. There was no question in regard to the diagnosis, which was tumor of the internal popliteal nerve. I regret, however, that a careful study of the nervous phenomena was not made.

On January 28th I made an incision over the tumor and found it to be situated within the internal popliteal nerve, the fibers of which were spread over it. The cut revealed many tumors involving the sciatic nerve and its internal and external popliteal branches. The incision had to be continued upwards to the lower border of the gluteal mass of muscles. The whole length of the sciatic nerve from the sacrosciatic foramen was studded with tumors varying in size from an eighth of an inch in diameter to about an inch and a half in diameter. The external popliteal and internal popliteal nerves were also involved. I removed in all about thirty-six of these growths. They were evidently developed from the connective tissue in the nerve trunk and the nerve fibers were separated by them and spread over their surfaces. The

tumors appeared to be fibrous in character, but many of them were wholly or in part of a gelatinous consistence, as though the fibroid tissue had undergone a myxomatous change. The fifteen-inch incision, which extended from the buttock to the lower extremity of the popliteal space, was closed with twenty-six catgut sutures and an aseptic dressing applied. The patient had practically no pain after the operation. The wound healed by first intention. No marked numbness of the foot remained, and when discharged from treatment he had good motion in all the toes.

No accurate examination of the areas of anesthesia and no determination of the electric reaction of the muscles was made. Some of the nerve fibers were undoubtedly injured in the excision of these tumors, though as far as possible the nerve sheath was split and the nerve fibers separated in a longitudinal direction.

The microscopic examination showed the tumors to be fibromas.

An interesting report of tumors of the sciatic nerve will be found in the *Twentieth Century Practice of Medicine*, vol. ii, p. 333. This article, written by Dr. James Hendrie Lloyd, showed me that the condition was rarer than I had previously supposed. It is very much regretted that circumstances prevented me having the benefit of Dr. Lloyd's examination of the case before operation was undertaken. The careful study of the neurologic features of the patient would have been valuable, though it would not have influenced in any way the character of the operation.

February 28, 1901.

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### Venous Angioma of the Flexor Muscles of the Fingers.

JOHN B. ROBERTS, M.D.

A man, aged twenty-four years, was operated upon at the Polyclinic Hospital, on February 11, 1901, for a swelling about the middle of the forearm, on the palmar surface, which had recently become the seat of pain. He said that he had injured the arm when he was twelve years of age and that the swelling had been there since that time. According to his statement the growth had slowly enlarged, but had not interfered with work and had given him no pain until recently. On grasping the forearm and having the patient move

his fingers there was a vibratory sensation perceived by the hand of the examiner similar to that observed in tenosynovitis. The elasticity of the swelling resembled that of a tense thecal cyst. The tumor was situated in the middle of the palmar surface of the forearm and was about three inches long and an inch and a half wide. A longitudinal incision through the skin, made under anesthesia, revealed a venous angioma involving the superficial and deep flexors of the fingers. The entire thickness of these muscles was involved, as was shown by carrying the finger beneath the muscle. The venous channels were developed in the muscular masses and were separated by abundant fibrous tissue. The fibrous tissue was so great in amount that rolling the belly of the muscles between the fingers gave the sensation of hard particles within their structure. Examination before operation made me think that the condition was possibly a thecal cyst containing rice-like bodies. This was evidently due to the skin and superficial fascia slipping over the rough surface of the tumor. The rough surface was due to the irregularities produced by the hard, fibrous tissue and venous channels which made up the tumor. It was evident that the muscular tissue was riddled with fibrous partitions and venous channels.

The motion of the fingers was perfect. Careful examination of the mass showed that the tumor could not be removed without excising the entire thickness of the muscles for a space of about three inches. As this would have done an irreparable injury to the functions of the hand, the removal of the tumor was abandoned. One or two incisions were made in the mass to see whether it was possible to enucleate it, and a small portion was removed for microscopic examination. Bleeding was very free, but after the application of sutures and a pad the arm was kept elevated and no further hemorrhage occurred. It was believed that the pain from which the patient had recently suffered would be relieved by the incision through the deep fascia which was necessary to expose the tumor.

The wound healed promptly, and the man when seen yesterday had good use of his fingers, though they were a little restricted by the fear of pain and the local induration at the seat of operation done sixteen days ago.



The pathologic examination, made by Dr. Guthrie McConnell, showed many bundles of voluntary muscle cut transversely. Between these fibers in many places was a large amount of connective tissue. In one portion of the specimen the muscle, having completely atrophied, had been replaced by fibrous tissue. In this same part were many large blood passages filled with blood. Many of the muscle fibers were much smaller than normal and their nuclei were no longer visible. In the region of the bloodvessels were numerous crystals, deep brown in color, apparently derived from the blood. There was no trace anywhere of malignancy.

In November, 1895, I reported to the Philadelphia Academy of Surgery a case of *fibro-angioma* situated beneath the four-headed extensor of the leg, and referred to the few cases of a similar character of which I could find mention. The paper was published in the *Annals of Surgery*. February 28, 1901.

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### Sarcoma of the Mediastinum of a Rhinoceros.<sup>1</sup>

RANDLE C. ROSENBERGER, M.D.

(From the Laboratories of the Jefferson Medical College Hospital.)

The material upon which this report is based was obtained from an Indian rhinoceros that died in the Philadelphia Zoological Gardens. The animal was believed to be near a century old, and was thought to have died from old age. There was no evidence of metastasis and the symptoms did not attract attention.

The specimen represents what is apparently a part of the pericardium, to which is attached a mass evidently of new formation. It consists of a slab of tissue measuring 30 cm. in length, 10 cm. in width, and 5 cm. in thickness. The incised surface is for the most part of a grayish or yellowish-white color; in some areas it is distinctly pinkish, in others dark brown. Upon one edge of the specimen is a comparatively smooth membrane 5 mm. in

<sup>1</sup> The writer is indebted to Prof. H. C. Chapman for the privilege of examining and reporting this case.

thickness, nearly pearly-white in color, to which the adjacent mass is adherent. There are also seen in the mass proper numerous large and small processes of glistening white tissue coming off from the above-mentioned membrane, giving the surface an appearance resembling that seen on section of alveolar structures. In consistency the mass is moderately soft, in some areas nearly pultaceous, the finger readily sinking into the softened areas upon the slightest pressure. In one or two small areas upon the membrane above mentioned there is a thin, irregular layer of what appears to be fibrin, evidently a part of existing inflammation. Small masses were taken for histologic examination.

These masses were fixed in absolute alcohol and embedded in paraffin. The specimen as a whole was preserved by Kaiserling's method.

Sections were cut and stained with hematoxylin alone, hematoxylin and eosin, hematoxylin and picric acid, toluidin-blue and eosin, carbol-fuchsin and methylene-blue.

Histologic examination shows the specimen to be made up for the most part of small round cells. Beside the cellular elements just mentioned there is a quantity of fibrous connective tissue which extends in a quite lawless manner between the round-cell elements. From these fibrous trabeculæ arise numerous more or less spindle-shaped cells that are distributed between the small round cells.

Numerous large and small bloodvessels are seen throughout the sections; they are distributed irregularly, and many of them possess no definite walls, being nothing more than sinuses limited by masses of the tumor cells. In other areas the bloodvessels are situated in the fibrous connective tissue; in this location infiltration of the vascular walls by round cells of the mass proper is clearly shown. Most of the vessels are empty, although a few contain erythrocytes and leukocytes. In those sections stained with toluidin-blue and eosin mast-cells or mucinoblasts are seen in the connective tissues. The areas upon the membrane that were thought to be fibrinous are seen to be made up of fibroblasts and small round cells. No cancer parasites were demonstrable. Pigment is present, being found in the tumor cells and in the connective tissue; it consists of small, brownish-yellow granules,

occasionally massed in groups approximating in size the volume of adjacent cells.

*Diagnosis.* Sarcoma, the predominating element of which is a small round cell; the quantity of pigment is hardly sufficient to justify our calling the neoplasm melanotic. *February 14, 1901.*

Original Specimens of Zygotes of Estivo-autumnal Malarial Parasites in the Middle Intestine of the Mosquito (*Anopheles Quadrimaculata*).

ALBERT WOLDERT, M.D.

Having become interested in the work of Ross, Marchiafava, Bignami, Celli, and Koch to determine the life history of the malarial parasite outside the human body and its mode of conveyance back to man, I began to study nearly two years ago the elementary principles of the subject by first learning the anatomy of the insect which had been charged with disseminating the infectious agent. The literature at this time was greatly scattered and needed revision badly.

After working for several months and then obtaining the aid of several friends among biologists and entomologists I finally succeeded in determining the anatomy of the mosquito. At this time I could find no dissection of this insect and there were no guides to follow; in fact, my guide was the anatomy of the blow-fly, but I had not made more than two or three dissections before I found that the anatomy of these two insects was totally different. In December, 1899, my first efforts to cultivate the malarial parasites in the mosquito were made, but, as is usual in first trials, proved entirely unsuccessful. This work was laid aside for several months, but in the spring of last year it was resumed, and after searching in various localities for the special genus of mosquito which is capable only (?) of acting as the intermediate host of the malarial parasite, I was, on June 19, 1900, rewarded by finding some larvæ of the *Anopheles quadrimaculata* and *Anopheles punctipennis*, both of which were found in the same pool of water. Subsequently visiting other localities where the history indicated

that such were endemic cases, I was able to discover five localities within the city limits of Philadelphia where these malarial-carrying mosquitoes have their breeding-grounds.

Since I had in the previous year treated a case of estivo-autumnal malarial fever about one-fourth of a mile distant from the locality where the first brood of *Anopheles* larvæ had been found, I decided in another instance to try and confirm the results of this observation.

On August 7, 1900, M. P., suffering with a double tertian infection, presented herself for treatment at the Howard Hospital, in the service of Dr. A. P. Francine, who kindly placed the case in my hands for study.

Obtaining an accurate history and learning from this that she had for several months previous to the development of her present illness been living in the neighborhood of Suffolk Avenue and Seventy-ninth Street, near Darby, and believing that the *Anopheles* could be found there if this were so, I made a special trip to this locality, and not only succeeded in capturing the adult insects but also found a breeding-ground of *Anopheles* about 300 yards distant from her residence. While there I learned that in nearly every house within a radius of half a mile there had been cases of malarial fever.

In another instance P. S., suffering with a single tertian infection, who had been admitted to St. Joseph's Hospital, in the service of Dr. M. T. Prendergast, and whose residence was in the neighborhood of Jefferson and Twenty-second streets, told me that she had only once within the past several months been away from home. On this occasion she had one evening about ten days previous to the development of her illness visited Woodside Park, at which time she was bitten by mosquitoes. Her home, it will be noted, was located near the center of the city, and the only collection of water where mosquitoes could breed was in the water reservoir a few squares away from her home. Believing, however, that the carrier of her infection did not come from this reservoir, but that the indications pointed toward Woodside Park as the source, I decided for the third time to test the law that "where there is endemic malaria there are mosquitoes" (*Anopheles*), and one afternoon I made a visit to this locality, and by accident found just below

the small lake located there a brood of *Anopheles* larvæ, some of which were taken home, and one was raised to the adult insect. It seems somewhat interesting to note that though I searched at least half a dozen other pools in this small stream of water, no other specimens were found. Other tests of this law gave the same results, and it must be admitted as a fact that *Anopheles* can be found in localities of this country where endemic malaria prevails.

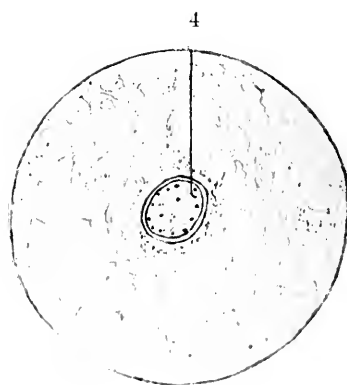
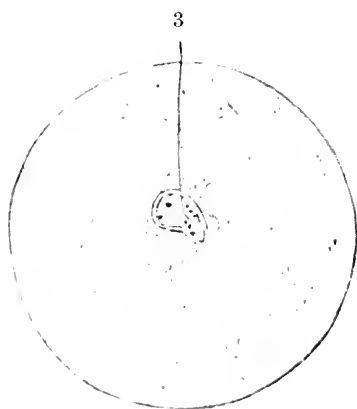
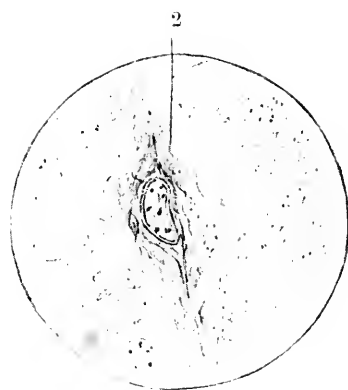
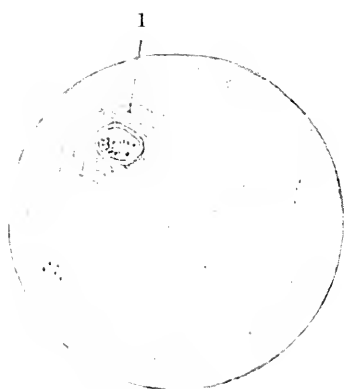
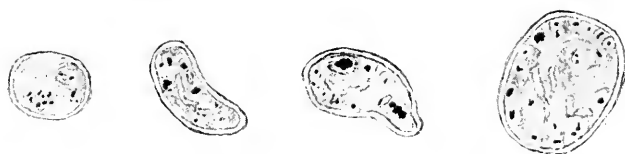
On the other hand, it must be admitted as a fact that *Anopheles* may be found in localities where there are no cases of malaria. While in the Pocono Mountains last summer our party was driven near a pool of perfectly clear water partly formed by a spring about fifty yards above. Here *Anopheles* larvæ were found. Since this was in an isolated spot quite remote from habitation and at an altitude of nearly 3000 feet above the sea-level, and since doubtless no case of malarial fever had been in that neighborhood, the adult insects were probably harmless.

Having in June, 1900, found the *Anopheles* in Philadelphia, my next efforts were directed toward determining whether or not these *Anopheles* were the malarial carriers, for at that time I was not aware that these specimens were identical with the *Anopheles claviger*, or, better, *maculipennis* or *quadrimaculata*, which had been used by Ross, Koch, and the Italian observers.

In July, 1900, Dr. J. C. Wilson very kindly offered me the opportunity of studying a case of tertian malarial fever in the wards of the Pennsylvania Hospital. This was my second trial, and, like the preceding one, proved a dismal failure. Three, four, five, six, seven, eight, and nine attempts proved equally unsuccessful.

Having had some correspondence with Dr. Ronald Ross on this question, this observer very kindly sent to me for inspection a specimen of the middle intestine of a mosquito containing the zygotes of proteosoma, or bird malaria, which I had the pleasure of exhibiting before this Society in November last.

It was now the 27th of October, 1900, and the malarial season had almost run its course, when a case of estivo-autumnal malarial fever was admitted to the Jefferson Medical College Hospital, in the service of Dr. Julius Salinger, who kindly placed the same at



my disposal. Two *Anopheles quadrimaculata* bit the patient, and one of these contained two zygotes, one of which is shown under the microscope. Accurate drawings of these coccidia have not yet been made.

These specimens, however, were not discovered for several days after dissection and not until after another case of estivo-autumnal malarial fever had been offered me for study by Dr. Frederick A. Packard, which occurred in his service at the Pennsylvania Hospital, and to whom I feel very grateful. In the latter instance seven *Anopheles quadrimaculata* bit the patient, five of which were afterward dissected, but only one seemed to have been infected. In this specimen four zygotes in different stages of development were found on November 5, 1900, one of which may be observed under the microscope.

In both instances the insects after biting were placed in a wooden box covered over with gauze, and afterward kept from three to four days at a temperature of about 78° F. and then dissected. The laboratory facilities for doing this work were

#### EXPLANATION OF PLATE.

From the case of Dr. F. A. Packard, occurring at the Pennsylvania Hospital.

Four zygotes (unstained) of estivo-autumnal malarial parasites in different stages of development and found in lower portion of middle intestine (stomach?) of *Anopheles quadrimaculata* (or *claviger*). The mosquito bit on Thursday, November 1st, 8 to 9 P.M., and was dissected on the Monday following. No. 3 oc. No.  $\frac{1}{2}$  oil immersion (Leitz).

No. 1.—Ovoid-shaped zygote in an early stage of development and containing numerous reddish pigment-granules and vacuoles. About 14-16  $\mu$  in diameter.

No. 2.—Crescent-shaped zygote, containing reddish pigment-granules and growing between muscular fibers, which it pushes to either side. The pigment-granules are of larger size than in No. 1 and are pressed toward the periphery. About 14-16  $\mu$  in length.

No. 3.—More or less vesicular-shaped coccidium, containing bright reddish pigment-granules and slit-like vacuoles. The body of the coccidium has a faint yellowish tint. About 10  $\mu$  in diameter and 14-17  $\mu$  in length.

No. 4.—More or less ovoid-shaped zygotes, containing numerous reddish pigment-granules of destroyed hemoglobin, which are arranged around the periphery. Numerous slit-like vacuoles are also shown. About 12-14  $\mu$  in diameter and 16-20  $\mu$  in length.

Figures 1, 2, 3, and 4 greatly magnified.

generously tendered me by Dr. Simon Flexner, to whom I am greatly indebted for very many favors.

While these specimens of zygotes cultivated in the Anopheles which had bitten the last case at the Pennsylvania Hospital were the first I had seen, I was able to identify them from the surrounding cells from their *delicate hyaline capsule*, their clear and vacuolated appearance, characteristic shape, disposition among the muscular fibers and epithelial cells, and, above all, from their contained *reddish pigment-granules* of destroyed hemoglobin obtained from the erythrocytes of the human blood.

It gives me much pleasure to exhibit these specimens before you, which, I believe, are the second successful series so far obtained in America, the first having been made by Dr. W. S. Thayer, of Baltimore, but whose specimens have most unfortunately been destroyed.

February 14, 1901.

#### Extensive Thrombosis of the Sinuses of the Brain.

JAMES HENDRIE LLOYD, M.D.,

AND

FREDERICK A. RUPP, M.D.

Thrombosis of the sinuses of the brain is not such a rare condition that we should care to show an instance here this evening unless it were one of very exceptional interest. These cases are usually divided into two classes, primary and secondary. Primary thrombosis is that which occurs in some of the debilitating diseases, such as tuberculosis in its last stages, the dyscrasia of syphilis, infantile diarrheas, and occasionally in chlorosis. In these cases there is no disease of the contiguous bone. The secondary form is that which occurs as a result of disease in the neighboring bone, the most common instance being that seen in diseases of the middle ear, in the petrous portion of the temporal bone. The present case is an instance of this secondary thrombosis occurring in a woman who had long-standing ear disease which was supposed to have been latent or quiescent for many years. Its



especial interest consists in the fact that the thrombus had extended far from its original seat and had caused beginning softening in some of the basal structures of the brain.

Mrs. J. R., aged thirty-four years, was brought to the hospital December 22, 1900, her case having been diagnosed before her admittance as one of typhoid fever.

Her family history was negative. The patient had had measles when a child, with "running ears." During early childhood she became deaf in both ears; at the age of eight years her right eye was removed for a tumor, the nature of which is unknown. Otherwise she was in fairly good health up to the present illness.

Her illness began about seven days before her admission to the hospital. It began with vague aches and pains and a feeling of fever and a headache. There was some cough, but no expectoration. She felt ill and had a diarrhea. There was no epistaxis. Abdominal pains were quite marked.

Physical examination showed heart and lungs normal; no typhoid rose spots or abdominal distention; abdominal gurgle present; spleen not enlarged; Widal and diazo tests both negative; abdominal tenderness marked. Urine alkaline, albumin present, also hyaline and granular casts. After a few days in the hospital the condition of the kidneys improved.

Examination of blood: Red cells, 4,460,000; white cells, 10,600; hemoglobin, 78 per cent.

Four days after entering the hospital the patient became comatose; the bowels and bladder were evacuated involuntarily. Examination of the eye-ground was negative. There was no discharge from the ears. The patient remained comatose until the time of her death, December 29, 1900.

*Autopsy.*—No gross lesions were found in the thoracic, abdominal, or pelvic cavities.

Upon removing the brain and the dura a chicken-fat clot was found in the right lateral sinus; other lesions of the brain are shown in the specimen.

As will be seen in examining this specimen, the thrombus extends back through the lateral sinus to the torcular herophili, then extends forward through the straight sinus, which it distends, making a solid mass of it projecting upward between the

occipital lobes of the brain. The veins of Galen are also greatly distended as well as some of the veins of the right lobe of the cerebellum. The posterior part of the optic thalamus (pulvinar) is the seat of beginning softening. It presents the mulberry discoloration described by some authors. For some reason this softening is found only in the right optic thalamus. In fact, the right side of the brain is the most involved in this whole process.

*February 14, 1901.*

### An Unusually Large Nasal Polyp.

T. R. CURRIE, M.D.

I am indebted to Dr. Joseph S. Gibb for the privilege of exhibiting this specimen. It was removed by him at his clinic at the Protestant Episcopal Hospital of this city. The patient was a young man, aged twenty-three years, and for three years had been complaining of nasal obstruction and a "feeling as if there were something at the back of his throat." He also gave a history of snoring and sleeping with his mouth open. The patient has the facial characteristics of a mouth-breather.

The tumor, which is of the fibromyxomatous variety, seemed to have its origin in the posterior portion of the right middle turbinal. It filled the entire nasopharynx, and was adherent to the septum posteriorly and also to the pharyngeal vault.

On account of its size and location its removal was attended by considerable difficulty; indeed, its size is the only excuse I have to offer for encroaching upon your valuable time.

It measures in its long axis  $2\frac{1}{2}$  centimeters, at its widest horizontal axis 2 centimeters, and where these lines bisect each other its diameter is  $1\frac{1}{2}$  centimeters.

*February 28, 1901.*

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# Proceedings

of the

## Pathological Society of Philadelphia.

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### Trichinella Spiralis, Trichinosis, and Trichina-inspection: A Zoologic Study in Public Hygiene.<sup>1</sup>

CH. WARDELL STILES, PH.D.,  
WASHINGTON, D. C.

MR. PRESIDENT, LADIES AND GENTLEMEN: Disease may be viewed from various stand-points. The pathologist and the zoologist are inclined to consider it theoretically; the practising physician from the more immediately practical stand-point of treatment; the patient from a more personal position, disapproving of anything which causes him pain; the State from the economic side, in that efforts are made to counteract factors, including disease, which tend to have an unfavorable effect upon the well-being of the country.

In selecting a subject upon which to address you this evening, it has seemed to me appropriate to refer to a certain medico-

<sup>1</sup> Address delivered by invitation at the Annual Conversational Meeting of the Society, April 25, 1901.

zoologic discovery made in Philadelphia about half a century ago and to briefly bring to your attention the important bearing which this observation has had not only directly upon medicine, from the stand-points of the patient, the physician, the pathologist, and the zoologist, but also upon public hygiene, national economics, and our diplomatic relations. This will take us for a time away from our abstract studies and remind us that the work of the medical and scientific professions is not confined to the sick-room and laboratory.

One day in 1847 the late Professor Joseph Leidy, while cutting a slice of cold ham for the purpose of making a sandwich, noticed a peculiar appearance which he recognized as abnormal. Placing a small piece of the meat aside, for later examination, he continued his meal.

This was an insignificant incident in itself, but an observation Leidy made upon the meat has been of great zoologic, medical, hygienic, economic, and political importance. That ham sandwich resulted eventually in differentiating from typhoid fever a disease which had formerly been confounded with this malady; it eventually gave rise to a special occupation which furnishes employment to between 40,000 and 50,000 people; it has resulted in the sale of probably more than 100,000 microscopes for use by persons who would otherwise never have worked with this instrument; in the last analysis it was the basis for the prohibition of the importation of American pork in Germany for about nine years; it gave rise to a bitter political fight among German political parties; it cost the farmers and exporters of the United States millions of dollars; it saved hundreds of human beings from an excruciating disease and death; it resulted in what is proportionately probably the most expensive system of public hygiene which has ever been put into practice, a system in regard to the value of which opinion is divided; it was to a certain extent one of the most important factors in the rapid strides in the discoveries of the etiology of disease, in that it stimulated investigation in this line; upon it have been based numerous laws, decrees, orders, and police regulations; it has sent many a man to prison; it gave rise to one of the most important and prolonged diplomatic correspondences which our Government has had to consider in recent years; it has resulted in the use of more printer's ink and paper

than any other medical or zoologic subject, with a few exceptions, which has ever arisen. All of these things had their origin in a Philadelphia ham sandwich, worth certainly not more than ten cents.

The factors involved form one of the best-known illustrations of the influence of zoology in medicine and economics, in public health and public policy, and as I was specially requested to speak upon some medicozoologic subject, I have chosen Leidy's ham sandwich as my text. I am further led to do this because it enables me to present to you some important unpublished medical statistics, and to thus place you in a better position to judge a certain proposition occasionally urged, namely, that we should introduce into this country the obligatory microscopic inspection of pork; finally, by selecting this subject, I am able to refer to a discovery made by one of your most esteemed and most honored friends, the late Joseph Leidy.

As Leidy was on the point of preparing his ham sandwich for its process of evolution into human protoplasm, his keen eyesight discovered some minute structures in the meat. His scientific curiosity got the better of his appetite, and his microscope and knowledge of medicozoologic literature enabled him to recognize in these minute specks a small worm now known to you all as *Trichinella spiralis*. Owen had described this helminth in 1835 from specimens found in a human cadaver by a medical student in London; it was found in man on several occasions, but was generally looked upon more as a zoologic curiosity than as the cause of a serious disease.

Later a German physiologist, Herbst, found the same species of parasite in dog, and feeding the meat to a badger, and then the flesh of this badger to some dogs, he showed that the worm could be transmitted through the food.

In 1860 Zenker, of Dresden, diagnosed as typhoid a case of disease in a girl. The patient died, and postmortem examination failed to exhibit the pathologic lesions he expected to find; on the contrary, he found the same species of nematode present which Owen had described in 1835, and which Leidy had found in his ham sandwich. Leidy's ham sandwich was a clew, and Zenker proved himself a worthy Sherlock Holmes. Inquiry showed that other members of the girl's family also had been sick and that

they, too, had eaten pork, while investigation revealed trichinæ in the remnants of the meat.

Thus was a newly recognized disease brought to the serious attention of the medical world, and the ham sandwich of a Philadelphia zoologist showed not only the source of infection, but also gave a clew to the proper methods of prevention.

Some antivivisectionists maintain that experiments upon animals have resulted in no appreciable good, but Herbst's experiments, following the discoveries by Owen and Leidy, gave to Leuckart, Virchow, Zenker, and others the direct clew which when followed out resulted in placing public hygiene in a position to propose methods of prevention which have unquestionably saved thousands of cases of disease and prevented hundreds of deaths. Assuredly it would be an inhumane and inhuman act, hardly to be expected of a rational being, to hold that the lives of Herbst's dogs or those of the rabbits used by Leuckart and others were of more value than the human lives which have been saved since 1860 by means of knowledge gained from those experiments.

From 1860 to 1870 came the noted trichina years of Germany, when not only the daily press but also some of the professional organs indulged in a panicky hysteria, expressing views which seem absurd to us to-day, but perhaps not more absurd than some of the views of this last decade will appear to scientific workers in 1950.

During the seventies, American exporters began to compete in Europe in the sale of pork with the European producers. Leidy's ham sandwich and the subsequent examination of American pork in Europe gave to agrarian agitators a supposed hygienic argument against this competition; by a very questionable use of the hygienic flag a political purpose was accomplished, and American pork was excluded from Germany on May 6, 1883, the interdiction lasting until September 3, 1891. Germany's example was followed by France, in spite of the repeated reports of the French Academy of Medicine and the Consulting Committee of Public Hygiene, to the effect that such an interdiction was not justified by sound hygienic arguments.

It is difficult to estimate the exact financial loss to our country caused by this alleged hygienic measure, as the amount of exports is naturally influenced by the varying amount of home production

in the import countries. A conservative estimate, however, would place the loss in the millions of dollars.

The Continental prohibition of an article of diet used by the masses should teach us an important lesson in public hygiene. That lesson is that any measure of this kind not justified on hygienic grounds, but forced under the hygienic flag, is calculated to result not only in a total suppression of the trade, but on the contrary in forcing the traffic out of the hands of honest firms into the hands of smugglers and underhanded dealers. The grounds advanced for this prohibition, alleged to be necessary from the stand-point of public hygiene, were so weak and contrary to experience, and were so ably exposed by leading hygienists, whose motives were above suspicion, that they failed to carry conviction among the masses. As a result many dealers in England, Holland, and Belgium continued to import American pork and to re-export it to the prohibiting countries as European products, and the workingman continued to purchase it at a higher price than he would have paid under other conditions.

The impossibility of stopping this traffic should be a lesson to us all, that if we wish to put into effect an extreme hygienic measure, we must first not only be sure of our grounds, but we must have arguments of such a character that we can convince fair-minded people of the justice of our views, so as to have their support in suppressing attempts to circumvent the regulations imposed.

In 1891 the Imperial German Government withdrew its prohibitory decree, and the German meat market was again open to the American exporter. This naturally met with the opposition of the Agrarian party, and a Prussian ministerial decree was issued on May 21, 1892, which practically called upon the local authorities to introduce local restrictive measures of an alleged hygienic nature. It was claimed that American pork which bore our certificate of inspection was not properly inspected. It has been one of my duties to investigate these charges, and after a most careful study of all the factors involved, I cannot escape the conclusion that the primary trouble was in the German customs-houses. The statement in the Prussian decree of 1892 that some of our pork contained trichinæ was unquestionably correct, but I find that certain of the customs officials on the German border did not understand their duty, and accepted certificates of

inspection which were intended not for Germany but for other countries and for interstate trade where a trichina inspection is not required. Furthermore, there was a laxity in regard to accepting certificates which enabled smugglers to present the "original" with inspected meats at one custom-house, and the "duplicate" with uninspected meats at another.

Thus the American meat inspectors had to bear the blame for the carelessness of Continental customs officials. Other factors also were involved, but a full discussion of these would carry me far beyond the limits of an evening address.

Let us now turn to a practical hygienic side of the problem: What has been the actual effect of this meat upon the health of Germany as shown by the German sanitary statistics?

An inquiry of the kind I propose is important in more ways than one. It involves the practicability of the operation of one of the most expensive systems of public hygiene ever suggested. Demands are occasionally made that we shall introduce this system as obligatory in the United States, and before we take our stand either for or against we should know what benefits have accrued from it in Germany. To understand the question so that we may form a tenable judgment upon it we must inquire into the life-history of the parasite, the method of inspection, the number of inspectors required, the cost of the inspection, the results of the inspection, and the number of cases of trichinosis which occur when there is no inspection.

It will hardly be necessary to review all the biologic details regarding this parasite. You will recall that it presents three stages: (1) Adult males and females in the intestine; (2) small embryos are born which wander to the muscles and here become (3) encysted larvæ. Hogs contract this parasite by eating infected rats or infected scraps of meat in offal or swill; rats contract the worm by eating each other or by eating scraps of infected pork or flesh from human cadavers, as, for instance, in dissecting-rooms; man contracts the disease usually from eating pork which is not properly cooked or sufficiently cured.

From a stand-point of therapeutics you will recall that when the parasite has once left the lumen of the intestine for the other parts of the body specific treatment is unknown. You will recall further that mortality is highest between the fourth and sixth



weeks. The death-rate varies from 0 to 100 per cent. Of the 14,820 cases of the disease, which I have collected from German literature as occurring in the empire during the years 1860-1898, there were 831 deaths, giving a mortality of 5.6 per cent.

Having practically an untreatable disease, it is incumbent upon us to try to prevent it. How can this best be done? The American Governmental officials in question tell you to educate the people to avoid eating pork which is not thoroughly cooked or cured; to do away with the offal feeding of hogs, and to regulate the country slaughter-house. The German Government, on the other hand, calls for a microscopic inspection of the pork before it is sold. Some Americans point to the German inspection and urge its introduction here. Some Germans point to the comparatively few cases of this disease reported for America and want the German people to be educated to cook their pork.

It is not my purpose to offer advice to Germany this evening. She has a wide-spread folk's custom to deal with, the custom—or as it has been aptly named, *Unsitte*—of eating raw pork. Folk's customs are more easily strengthened than done away with. I believe the German inspection is a system *par excellence*, calculated to strengthen the *Unsitte* referred to, but that is not my affair so far as it applies to Germany. It is, however, my privilege to argue against introducing either this *Unsitte* or the microscopic inspection into our country, or rather to warn against allowing the *Unsitte* to spread, for I have recently visited certain places in Texas where raw pork is eaten with a true Saxon or Prussian relish.

The German microscopic inspection consists of taking samples from certain muscles, notably the diaphragm, psoas, and tongue, compressing them in a so-called "compressor" and examining the preparations microscopically.

For this purpose Prussia employed in 1896 an army of 27,602 registered microscopists (more than there were enlisted men in the United States Army at that time), making 1 trichina inspector to every 1176 inhabitants. If these statistics of 1896 are extended to the total number of inhabitants in the German Empire at about the same date, given December 2, 1895, at 52,279,701, we find that, assuming the same conditions, 44,455 microscopists could have been employed. At this same rate we would require for the United States an army of nearly 65,000 microscopists.

In connection with these figures, and especially in connection with the outbreaks of trichinosis, we should hold in mind an important fact which is almost universally overlooked, namely, that these inspectors must be divided into two general classes; *first*, those microscopists who give up practically their entire time to the work, and are stationed at regular inspection offices, such as in slaughter-houses and abattoirs, where they are under the constant supervision of a higher inspector; and *secondly*, those inspectors who follow some other line of work as a vocation (physicians, druggists, teachers, butchers, blacksmiths, etc.) and who take up trichina-inspection simply as an incidental source of income. For the most part, the men and women of the second class are scattered over the country and country towns, work independently, and, although regularly licensed to do this work, are not subject to daily control, but like the workers of the first class are subject to a triennial re-examination as to fitness for their work.

It is difficult to give an exact estimate of the cost of this inspection. Taking various statistics as a basis, we would obtain for the German Empire figures varying between \$2,276,862 to \$7,089,772. An average based upon four different computations gives \$3,792,577 as approximately the amount it would probably cost Germany to introduce a general inspection—and in this estimate I omit the general economic loss to the country caused by the condemning of meat, also the cost of instruments, light, fuel, heat, stationery, etc.

While these figures cannot be accepted as exact, it does not appear probable that it would annually cost our country less than \$3,000,000 or \$4,000,000 to introduce the inspection here.

If conditions were such that all the hogs could be slaughtered at regular abattoirs, the expense would be much less, for we would then employ only inspectors of Class 1, who could be paid by the month. Such a plan, however, is impracticable, since many small towns and farms kill for local consumption, hence we should have to appoint thousands of inspectors of Class 2 and pay them by piece-work. To institute the inspection for the cities and to omit it for villages and country districts would be absurd, for it is particularly in the country and villages that our American cases of trichinosis have occurred.

As to the frequency of trichinosis in America, it is unfortunately impossible to give as complete statistics as I have collected for Germany. I have records of about 900 cases for the United States for the years 1860 to 1895. Undoubtedly the disease is more common with us than would appear from these figures. It does not in fact seem unreasonable to assume that many cases diagnosed as atypical typhoid or as rheumatism are in reality cases of trichinosis. We know that trichinosis is present in about 2 per cent. of the American hogs. We have numerous persons in the States who are of Prussian or Saxon origin, and many of these have brought their raw-pork *Unsitte* with them. Still, we are undoubtedly justified in the conclusion that in America we have had fewer epidemics of this disease than have occurred in Germany, and that most of our cases have been more or less isolated or at most, as a rule, very small outbreaks confined to one or two families.

It is interesting to note that of 274 American cases where I obtained the nationality of the patients about 76 per cent. were Germans.

TABLE OF NATIONALITY OF 274 AMERICAN CASES.

German . . . . .	203 cases	" French Canadian " . . . . .	3 cases
" Foreign " . . . . .	37 "	" French descent " . . . . .	1 case
Negro . . . . .	10 "	Hungarian . . . . .	1 "
Italian . . . . .	4 "	Dane . . . . .	1 "
Irish . . . . .	4 "	Swede . . . . .	1 "
American . . . . .	4 "		

Let us now recall that for the years 1892-1898 the United States exported to Germany in the neighborhood of 237,000,000 or more pounds of pork. Nearly all of this was "cured" before shipment. Let us admit for the sake of argument that less than half of this was reinspected in Germany, and that this was trichinous in the same percentage as the Germans claim for the pork which they did reinspect. How does the American curing process compare with the German inspection as a method of public hygiene, judged from the statistics collected for Germany?

The German statistics in question have been collected from published records, and I can give if necessary the exact page and place of publication of every case referred to. In order not to make an unfair comparison, I will quote only the statistics for the

years 1881 to 1898 inclusive. The records prior to 1881 are too incomplete for satisfactory study. The statistics subsequent to 1898 I feel compelled to reject *in toto*. This I do not from a prejudiced stand-point nor speaking as a Government official; but from a purely scientific point of view I am unable to attach much importance to records published under the influence of the following very remarkable decree, which was issued as confidential but was afterward read from the rostrum of the German Reichstag by one of the members of that legislative body:

[TRANSLATION.]

C. B. 2323.

"THE DISTRICT PRESIDENT.

" DUESSELDORF, July 24, 1899.

"According to a circular of June 11, 1894 (*Ministerial Journal for Internal Administrations*, p. 102) inquiries and requests which are directed to German administrative authorities by consuls of foreign States, stationed in Germany and provided with exequatur, so far as lies within their (the consuls') official duties and within their official district, can be answered by these (German officials) directly, in so far as the questions are not matters of general policy (importance). Toward the American Consuls, for whom the foregoing principles are also valid, all communications are, however, to be avoided which are likely to work against German interests, immaterially whether their desire for information bears upon questions of general policy (importance) or not. In cases of doubt, an answer is at first not to be given, and report to be made to me. As information, which under no circumstances is to be given to American Consuls, I designate, for instance: statistical data regarding violations of the Imperial food law (*Nahrungsmittelgesetz*) and its supplementary laws, especially regarding the manufacture of and trade in foods and edibles which are injurious to health, including toys, regarding adulteration (falsification) of and trade in such wares, and the trade with such adulterated (falsified) wares, *regarding the finding of the trichinæ and cysticerci in native pork, and regarding the status of disease in man and animals*. Whenever the questions for information touch the last-named points there is, however, no objection (hesitation) for German officials to refer to the regular statistical reports in the *Veroeffentlichungen des Kaiserlichen Gesundheitsamtes*; no further material is, however, to be furnished.

"I request you to treat this matter as strictly confidential and to provide the officials under your charge with appropriate instructions, laying particular stress on the *strictly confidential* treatment.

"A communication of this order to the Mayors through simple repetition of this in copy is not to take place; you are rather to act by giving special orders.

"(Signed) FREIHERR VON RHEINHABEN."

"TO THE LANDCOUNCILLORS AND HEAD MAYORS.

"(Favors to American Consuls are to be avoided, and in all cases not free from doubt report is to be made to the District President, A. G. I.)

"DISTRICT PRESIDENT."

Arranging the German statistics by years we have the following table, 1881-1882, being two years prior to the prohibition of

American pork, 1883-1891, nine years (with the exception of a few months) of the prohibition, and 1892-1898, seven years since the prohibition was annulled.

NUMBER OF CASES OF TRICHINOSIS AND DEATHS THEREFROM,  
1881 TO 1898 INCLUSIVE.

Year.	Prussia.		Saxony.		Other States.		Empire.	
	Cases.	Deaths.	Cases.	Deaths.	Cases.	Deaths.	Cases.	Deaths.
1881 . . .	387	10	177	1	3	0	567	11
1882 . . .	209	6	160	0	257	0	626	6
1881-82 . .	596	16	337	1	260	0	1193	17
1883 . . .	637	71	155	5	15	0	807	76
1884 . . .	348	29	73	2	50	0	471	31
1885 . . .	365	17	154	7	16	0	535	24
1886 . . .	136	10	47	1	20	2	203	13
1887 . . .	294	15	234	26	293	9	821	50
1888 . . .	134	14	404	34	18	0	556	48
1889 . . .	216	15	41	0	1	0	258	15
1890 . . .	96	0	117	0	9	0	222	0
1891 . . .	175	12	30	0	15	5	220	17
1883-91 . .	2401	183	1255	75	437	16	4093	274
1892 . . .	108	4	0	0	0	0	108	4
1893 . . .	28	1	0	0	10	0	38	1
1894 . . .	72	5	2	0	3	1	77	6
1895 . . .	358	4	3	0	1	0	362	4
1896 . . .	74	6	0	0	1	0	75	6
1897 . . .	141	6	2	0	1	0	144	6
1898 . . .	44	0	35	0	160	0	239	0
1892-98 . .	825	26	42	0	176	1	1043	27
1881-98 . .	3822	225	1634	76	873	17	6329	318

From this it is clear that a total of 6329 cases, 318 deaths, are reported during the 18 years in question, giving an average of  $351\frac{11}{18}$  cases,  $17\frac{2}{3}$  deaths per year. The mortality of the disease in Germany for 18 years was about 5 per cent.

The table also shows that there has been a general decrease in trichinosis in Germany during recent years. This may be interpreted as being due to several causes, of which the following are the more important :

1. The general education of the public by warnings on the part of police and other authorities that the inspection should not be relied upon too implicitly, but that pork should be well cooked.

2. The microscopic inspection, by removing from market about 1400 to 3100 trichinous hogs per year, naturally reduces the chances of infection for those persons who do not heed the warnings by the authorities and the lessons taught by previous epidemics.

The disease is still encouraged by the following circumstances :

1. The exceedingly dangerous custom of eating raw or rare pork. The sale of raw pork in public restaurants and railway restaurants is not calculated to decrease this custom.

2. The trichina inspection, while diminishing the chances of infection in one way, at the same time gives rise to a false feeling of security among many people ; since the latter erroneously believe that if the pork has been inspected they may eat it raw without the slightest danger of infection. Even persons who have suffered from trichinosis are occasionally found who now have implicit faith in the inspection.

It appears exceedingly doubtful whether Germany will ever be entirely free from this disease.

A classification of the cases based upon the source of infection is exceedingly difficult, since a number of outbreaks are reported with details which are insufficient to permit a definite judgment, and since numerous German laws and regulations must be constantly held in mind. When the report says that the inspector was discharged or imprisoned, it may be assumed that the meat was inspected or its non-inspection was due to carelessness ; when the report states that it could not be determined which of several inspectors examined the meat, this may be interpreted as meaning that the meat was examined. It must be admitted that if several persons examined the published evidence independently some of the cases reported in a careless manner might be placed in different groups. All that can be demanded of the compiler is that he shall exercise good faith in attempting to interpret the reports. If reports are equivocal, or if authorities disagree, any error of classification, if discovered, should be charged to the original reporter for not making his statements more intelligible.

A classification of the cases and deaths arranged according to the source of infection is shown in the following table :

SUMMARY FOR GERMAN EMPIRE, 1881-1898.

1881-1882.		1883-1891.		1892-1898.		Totals.	
Cases.	Deaths.	Cases.	Deaths.	Cases.	Deaths.	Cases.	Deaths.
1193	17	4093	274	1043	27	6329	318
314	4	1262	103	466	5	2042	112 <i>a</i>
89	.....	42	10	11	3	142	13 <i>b</i>
272 [675]	..... 4]	641 [1945]	4 117]	291 [768]	3 11]	1204 [3388]	7 <i>c</i> 132 <i>d</i>
.....	.....	63	.....	.....	.....	63	..... <i>e</i>
199	1	589	76	86	7	874	84 <i>f</i>
195	3	896	61	79	6	1170	79 <i>g</i>
30	.....	63	5	58	.....	151	5 <i>h</i>
77	6	595	15	45	2	647	23 <i>i</i>
17	3	1	.....	.....	.....	18	3 <i>k</i>
.....	.....	11	.....	7	1	18	1 <i>l</i>

Totals divided as follows:

*a.* Due to meat which, it would appear, was inspected and passed as free from trichinae.

*b.* Due to meat which was condemned, and usually buried, or was known to be trichinous, but was nevertheless used without proper safeguarding.

*c.* Due to other defects<sup>1</sup> in the inspection system.

*d.* Total cases and deaths which may be attributed to errors in the inspection system.

*e.* Additional cases may or may not have been due to inspected meat.

*f.* Definitely stated that meat was not inspected, or that no inspection existed; source of infection apparently known.

*g.* Source of infection known, but details regarding inspection not given, or insufficient to warrant conclusion.

*h.* Definitely stated that source of infection was not known or could not be traced.

*i.* No data given regarding meat, or data insufficient to classify.

*k.* Alleged to have been due to American meats.

*l.* Additional cases due to uninspected meat (of Russian origin).

<sup>1</sup> As "other defects" in the inspection system may be included: meat was eaten before results of the inspection were known; meat was inspected, but inspector suppressed the results of the examination; meat was stamped as free from trichinae before inspection was ended; meat was marked in the inspection book as free from trichinae; meat appears to have been smuggled around the inspection; inspector refused to examine meat; meat should have been inspected but was not; buried hog (inspected?) was dug up and eaten, etc.

In judging of the efficacy of the microscopic inspection, it is important to note that, according to the information at hand, 3388 cases with 132 deaths appear to have been due to the faults of the German inspection; this represents over 53 per cent. of the total (6329) number of cases and over 41 per cent. of the total (318) number of deaths. More than twice as many cases (*a*, 2042) and a third again as many deaths (*a*, 112) appear to have been traced to inspected meat, compared with the cases and deaths (*f*, 874-84) traced to uninspected meat; and even if all the cases from *e* to *l* inclusive are considered as to have been due to uninspected meat, this gives us less cases (3041), but more deaths (186), than have been traced to faults of the inspection (*d*, 3388 cases, 132 deaths). When these figures are compared with the (approximately) 900 cases collected for America (where we do not microscopically inspect our pork for home consumption)—cases extending over about twice as many years as cited for Germany—it cannot be admitted that the German microscopic inspection system is a hygienic measure which it would be well to introduce into this country. On the contrary, it would appear that it is much better for us to rely upon our methods of curing and cooking, rather than to expend between \$3,000,000 or \$4,000,000 annually to introduce a system which has a decided tendency to give the public a false sense of security, and, furthermore, a system which would unquestionably result in extending that exceedingly unhygienic German custom (*Unsitte*) of eating raw or rare pork.

In judging of the relations of American pork inspected before exportation to the German statistics, it is essential to notice that—

1. During the exclusion of American pork (1883-1891) Germany reports a total of 4093 cases, 274 deaths, giving an annual average of  $454\frac{7}{9}$  cases, with  $30\frac{4}{9}$  deaths.

2. Since its readmission (1892-1898) 1043 cases, 27 deaths, have been reported, giving an annual average of 149 cases,  $3\frac{6}{7}$  deaths.

3. Thus, as there has been an actual decrease of  $304\frac{7}{9}$  cases and  $26\frac{3}{5}$  deaths per year, it cannot possibly be maintained that American pork has caused any increase in trichinosis in Germany.

4. During the exclusion the source of the infection appears not



to have been established (or reported) in 588 cases, representing 14.3 per cent. of the 4093 cases reported.

5. Since the readmission the source appears (from present data) not to have been established (or reported) in 103 cases, representing 9.87 per cent. of the 1043 cases reported.

6. This reduction in the percentage of cases of unestablished or unpublished sources would seem to indicate that since American pork has been used in Germany the authorities have increased their efforts in tracing the origin of infection.

7. And if with this apparently increased vigilance 940 cases, or 90.12 per cent., have been traced, *and not a single one of these has ever even been alleged to have been due to American pork*, it would not appear justifiable for anyone to advance the claim that the remaining 103 cases (average of  $14\frac{5}{7}$  cases per year, or 9.87 per cent.) were due to American meat.

8. Especially is such a claim not justifiable in view of the fact that during the exclusion of our products 588 cases (average of  $65\frac{1}{3}$  cases per year, or 14.3 per cent.) occurred, the source of which is not given.

9. It cannot, therefore, be admitted that the systematic attacks upon American pork found in the German agrarian press find any support in the accessible German health statistics.

10. Of the 17 cases, 3 deaths, which are alleged to have been due to American pork in 1881, it may be remarked that Virchow, the leading pathologist in Germany, and Fraenkel, one of Germany's leading sanitarians, have not admitted the evidence as valid; nor is the evidence accepted by Hertwig, Brouardel, or Wasserfuhr. The case in 1883 is not claimed to have been contracted in Germany.

11. Thus it must be submitted that the sanitary quality, with reference to this disease, of American pork exported to Germany is vindicated by a summary of German statistics based upon German evidence.

12. And even the suggestion is not entirely unjustified that a total prohibition of the use of German pork in Germany and the compulsory use of American pork would probably do more to eradicate trichinosis than does their elaborate and expensive microscopic inspection.

It cannot justly be replied to this that the freedom from trichinosis due to American pork is accounted for by the German reinspection, for it may be conservatively estimated that not one-half of the American pork consumed has been reinspected in Germany. Furthermore, the fact that over one-half of the cases of this disease which occur are directly traceable to faults in the German inspection does not support the view that the reinspection is a very important factor in the case.

It is not my intention to maintain *that it would be absolutely impossible under any circumstances for a single case of trichinosis to arise in Germany from the use of American pork*; my claim simply is that a compilation of the German evidence fails to show that a single case of the disease has been traced to the more than 200,000,000 pounds of American pork exported to Germany during the fiscal years 1892-1898; and a study of the statistics does not support the view that the microscopic inspection gives a greater protection than do the curing methods. I am therefore forced to the conclusion that, from the practical experience of the German people with immense quantities of American pork, there is no sanitary justification for the numerous systematic and, too often, rabid attacks upon this article of diet which is so important to the thousands of German factory hands who live by the manufacture of articles exported to this country as well as to thousands of other Germans.

It might here be remarked that for about two years past there has been a standing offer in Germany, issued by an association of importers of American meats, of a reward of 1000 marks (\$238) for the first person who can prove a case of trichinosis in man in Germany due to American cured meats or sausages imported under the American certificate since 1891. Recent information is to the effect that no one has claimed the reward.

While I have incidentally mentioned the attacks which the German press has made on our meat, and while I have quoted these figures as proof that these attacks cannot be considered objective, that is not my chief reason for quoting the statistics. We have here important lessons in public hygiene. We find here an answer as to whether we should accede to the demands of the few and introduce into the United States a general compulsory

system of trichina inspection; such an inspection would virtually amount to a tax of \$3,000,000 to \$4,000,000 per year on the general public in order to gratify the palates of a few immigrants and their immediate descendants. We also have in these statistics an indication of the comparative values of curing methods and the microscope. Finally, we have a statistical summary of a disease in connection with which a Philadelphia ham sandwich and an observation by a Philadelphia zoologist have played an important rôle.

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### The Bacteriologic Examination of Clinical Thermometers.

RANDLE C. ROSENBERGER M.D.

*(From the Laboratories of the Jefferson Medical College Hospital.)*

The writer has been impressed with the fact that while surgeons, obstetricians, and many specialists recognize the necessity of guarding against infection by the sterilization of instruments used in operations as well as instruments of precision, the general practitioner not infrequently entirely neglects such precautions, and especially is this true of tongue depressors and thermometers. Upon inquiry many of the general practitioners have been found to make an attempt to limit infection by thermometers, resorting to some antiseptic or germicide kept in the thermometer case. While admitting the possible efficiency of such a method its routine use in the careless manner commonly adopted is probably more dangerous than no attempt at disinfection because an inefficient and unreliable method offers a sense of security not at all justified.

One physician whose thermometer the writer examined used a 1 per cent. solution of formalin with which he saturated a small pledget of cotton kept in the thermometer case. Another practitioner applied carbolic acid in a similar manner. Upon the examination, however, of these containers and the enclosed cotton neither formalin nor carbolic acid could be detected by odor, and the bacteriologic findings demonstrated their inefficiency. It is unnecessary to say that customary habit of simply rinsing a thermometer in water and wiping the instrument on a towel or handkerchief affords no protection.

A series of experiments have been made for the purpose of determining as far as possible in a small number of cases the probabilities of infection by means of a thermometer.

The method pursued was (1) to obtain the diagnosis of the case in which the thermometer was last used; (2) the time that had elapsed since the instrument was used; (3) how the thermometer was cleansed after using.

*Technic of Examination.* Having obtained the information indicated in the foregoing, the next step was to infect melted agar from which plates were made. The method of making plates was as follows:

A Petri dish was sterilized and half a tube of melted agar poured upon the bottom dish. With a sterilized glass brush (made sterile by passing directly through the Bunsen flame) the degree marks were thoroughly brushed upon the agar spread in the dish. The lid was lifted carefully and quickly, and as quickly replaced. In the remaining half of the melted agar in the tube the thermometer was rotated for a few minutes, then withdrawn, the tube agitated, and its contents poured into the dish containing the first part of the agar and the lid replaced. The plate was then allowed to set.

Inoculations were also made in bouillon by rotating the thermometer in the medium, which was then set aside for twenty-four or thirty-six hours, and when cloudiness appeared plates of agar were made. The results obtained by this method were used only for the purpose of establishing the character of the organisms present, being controls to the agar plates made as already described.

The next procedure was to observe how many colonies developed in the agar plates and what bacteria were present. The following is a detailed list of some of the examinations made and the results:

A thermometer used in a case of bronchopneumonia in a child was washed in cold water, dried with a handkerchief and examined two hours later. In forty-eight hours forty-six colonies had developed; seventeen of these were the staphylococcus pyogenes albus; two colonies were the staphylococcus pyogenes aureus; the remaining were sarcinæ and yeasts.

A thermometer used in a case of diphtheria was washed with cold water, dried with a handkerchief and examined forty-eight hours later. The plate yielded twelve colonies; seven of these were staphylococci (*pyogenes* and *aureus*), and the remainder were *sarcinæ*.

A thermometer used in a case of tuberculosis (pulmonary) was cleansed as in the foregoing, and examined forty-eight hours later. The plate developed one colony of the staphylococcus *pyogenes albus* and two colonies composed of *sarcinæ*. The physician from whom the thermometer was obtained used carbolic acid in the thermometer case.

From a thermometer that had not been used for forty-two days, and where the physician had forgotten the diagnosis of the case in which the instrument was last applied, there developed six colonies. Of these, two were staphylococci, one was evidently a member of the colon group, and three were *sarcinæ*.

A thermometer used in a case of rheumatism and immediately washed in a 5 per cent. solution of carbolic acid was examined seventy-two hours later, and yielded at the end of forty-eight hours' cultivation twelve colonies; three were the staphylococcus *pyogenes albus*; five *sarcinæ*; one *bacillus subtilis* and three of a chromogenic (pink) diplococcus.

A thermometer used in a case of pulmonary tuberculosis was washed in cold water and dried with a handkerchief, and examined by the writer fifty-six days later. In forty-eight hours fifteen colonies developed; four of these were staphylococci; six were *sarcinæ*; three *bacillus subtilis*; two chromogenic (pink) diplococcus

A thermometer used during the puerperium was washed with cold water, dried with a handkerchief and examined twenty-four hours after the last time it was used. Plates contained two colonies of the staphylococcus; four the *bacillus subtilis*; six of the *sarcinæ*, and four of the chromogenic (pink) diplococcus.

A thermometer was obtained from a physician who had used the instrument in a case of diphtheria, washed it in water and later took his own temperature, again cleansing the instrument as in the first instance. The writer examined the thermometer twenty-four hours later. The cultures yielded twenty-four colonies; six of the staphylococcus *pyogenes albus*; one of a *bacillus* which the

writer was inclined to regard as the pseudodiphtheria bacillus, and seventeen colonies of sarcinæ.

Without going further into the details of the examination in various cases, the following tables are submitted.

Table I is the result of the examination of thermometers used in the mouth, and Table II of thermometers used in the axilla.

TABLE I.

<i>Cases.</i>	<i>Length of Time After Using.</i>	<i>No. of Colonies.</i>	<i>Bacteria Found.</i>	
Bronchopneumonia,	56 days.	46	Staphylococci,	19 colonies.
			Sarcinæ,	27 "
Diphtheria,	48 hours.	12	Staphylococci,	7 "
			Sarcinæ,	5 "
Tuberculosis,	48 "	3	Staphylococci,	1 "
			Sarcinæ,	2 "
Rheumatism,	72 "	12	Staphylococci,	3 "
			Sarcinæ,	5 "
			Diplococcus (pink),	3 "
			B. subtilis,	1 "
Tuberculosis,	46 days.	15	Staphylococci,	4 "
			Sarcinæ,	6 "
			B. subtilis,	3 "
			Diplococcus (pink),	2 "
Puerperium,	24 hours.	16	Staphylococci,	2 "
			Sarcinæ,	6 "
			Diplococcus (pink),	4 "
			B. subtilis,	4 "
Diphtheria,	48 "	24	Staphylococci,	6 "
			Pseudodiphtheria bacillus,	1 "
			Sarcinæ,	17 "
Not given,	42 days.	6	Staphylococci,	2 "
			Sarcinæ,	3 "
			B. coli communis,	1 "

TABLE II.

<i>Cases.</i>	<i>Length of Time After Using.</i>	<i>No. of Colonies.</i>	<i>Bacteria Found.</i>	
Chronic indigestion,	24 hours.	4	Staphylococci,	3 colonies.
			Sarcina lutea,	1 "
Chronic indigestion,	3 "	14	Staphylococci,	12 "
			Yeast fungi,	3 "
			B. subtilis,	3 "
Chronic indigestion,	12 "	12	Staphylococci,	11 "
			Yeast fungi,	1 "
Chronic interstitial nephritis,	24 "	6	Staphylococci,	2 "
			B. subtilis,	4 "

<i>Cases.</i>	<i>Length of Time After Using.</i>	<i>No. of Colonies.</i>	<i>Bacteria Found.</i>
Gout,	48 days,	4	<i>B. subtilis</i> , 4 colonies.
Measles,	24 "	20	<i>Staphylococci</i> , 11 "
			<i>B. subtilis</i> , 5 "
			Unidentified bacilli, 4 "
Measles,	48 "	6	<i>Staphylococci</i> , 5 "
			<i>B. subtilis</i> , 1 "
Measles,	8 "	26	<i>Staphylococci</i> , 22 "
			<i>Sarcina lutea</i> , 4 "
Scarlet fever,	12 "	24	<i>Staphylococci</i> , 18 "
			<i>Sarcina lutea</i> , 4 "
			<i>B. subtilis</i> , 2 "
Scarlet fever,	24 "	18	<i>Staphylococci</i> , 12 "
			<i>Sarcina lutea</i> , 4 "
			<i>B. subtilis</i> , 2 "
Tuberculosis,	36 "	6	<i>Staphylococci</i> , 4 "
			<i>Sarcina lutea</i> , 2 "
Tuberculosis,	24 "	16	<i>Staphylococci</i> , 6 "
			<i>B. subtilis</i> , 4 "
			<i>Sarcina lutea</i> , 2 "
Tuberculosis,	72 "	2	<i>Staphylococci</i> , 2 "
Tuberculosis,	48 "	6	<i>Staphylococci</i> , 4 "
			<i>Sarcina lutea</i> , 2 "
Tuberculosis,	8 "	22	<i>Staphylococci</i> , 12 "
			<i>B. subtilis</i> , 8 "
			<i>Sarcina</i> , 2 "
Diphtheria,	24 "	4	<i>Streptococci</i> , 1 "
			<i>B. subtilis</i> , 3 "
Bronchitis,	72 "	6	<i>Staphylococci</i> , 4 "
			<i>B. subtilis</i> , 2 "
Bronchitis,	24 "	12	<i>Staphylococci</i> , 8 "
			Yeast fungi, 4 "
Bronchitis,	12 "	28	<i>Staphylococci</i> , 12 "
			<i>Sarcina lutea</i> , 10 "
			<i>B. subtilis</i> , 6 "

An examination of the results yielded by this investigation would satisfy the most skeptical that thermometers can readily transmit the bacterial flora found in the oral cavity. The writer is aware that for the satisfactory completion of this inquiry it would have been necessary to examine the secretions in the mouths of the patients upon whom the thermometers were used, and to have satisfied himself as to the character of the bacteria that they contained. There is another source of danger into which the inquiry did not extend, infectivity of thermometer cases, but as the case would only be a carrier, the essential danger, if any exist,

must be in the thermometer. In order to determine how readily thermometers could be disinfected the writer made nine experiments, using the following technic:

Immediately after removal from the mouth the thermometer was washed in water, immersed in corrosive sublimate for two minutes, removed from the antiseptic, dried in the air and replaced in the case. Later the instruments were examined, using the same technic as detailed above. The results of these experiments are given in Table III.

TABLE III.

<i>Cases.</i>	<i>Length of Time After Using.</i>	<i>Result.</i>
Rheumatism,	1 hour.	Sterile.
Chronic interstitial nephritis,	2 hours.	"
Croupous pneumonia,	1 hour.	"
Enteric fever,	3 hours.	"
Bronchitis,	2 hours.	"
Chronic indigestion,	1 hour.	"
Influenza,	2 hours.	"
Acute parenchymatous nephritis,	1 hour.	"

## CONCLUSIONS.

1. It is possible for the thermometer to be laden with the usual flora of the oral cavity.
2. Such bacteria may retain their capability of growth for an indefinite time, as shown by the above experiments, at least two months.
3. Many pathogenic bacteria possess similar capabilities, and it is not unreasonable to assume, although the above experiments are not conclusive upon this point, that transmission of bacterial disease by the thermometer is possible.
4. Thermometers are easily disinfected.
5. Where possible each patient should be possessed of a thermometer, as much his own property and as sacred to his own use as his tooth-brush.
6. Where for reasons of economy or otherwise it is impossible to carry out the recommendations expressed in conclusions 4 and 5, the thermometer should be disinfected before and after using.
7. The custom prevalent in the hospitals of keeping thermometers in disinfecting solutions is to be commended.

*April 11, 1901.*



### A Case of Pigmented Epithelioma of the Cheek.

M. B. HARTZELL, M.D.

Mary M., a domestic, aged forty years, sought treatment at the Skin Dispensary of the University Hospital for a small growth upon the right cheek beneath the eye and close to the nose. This growth was the size of a large pea, flat, dark brown in color, with a firmly adherent crust upon the summit, beneath which was a very superficial ulceration. The clinical history was extremely brief; it had lasted four years, beginning, in the words of the patient, "like a freckle," slowly and painlessly enlarging. A clinical diagnosis of pigmented epithelioma was made and excision advised.

A microscopic examination of sections of the excised growth showed that the greater part of the epidermis (in the center of the growth, all but the corneous layer), the papillary layer of the corium, and the parts immediately beneath it were replaced by a new growth composed of large round and oval cells with large nuclei, contained in round or oval alveoli, the walls of which were made up of a few slender fibrous bands. In some of the alveoli the cells were remarkably uniform in size and comparatively small, owing to the smallness of the cell body, the nuclei being quite as large as those contained in the larger cells. A very careful examination of the structure of the cells showed a very few in which faint traces of the prickles characteristic of the cells of the middle portion of the epidermis were still visible, but these were so very faint as to be easily overlooked. Throughout the neoplasm, but much more abundant in the lowest part of it, were many clumps of yellowish-brown pigment lying, for the most part, between the cells, but also within them, the intracellular pigment being in some cases so abundant as to almost completely obscure the cell structure. In some of the sections a few giant cells (two or three), with nuclei scattered irregularly through the cells, were observed. At the extreme margin of the growth the chief departure from the normal consisted in a widening of the epidermis, some vacuolation of the cells, and a marked accumulation of pigment in the lowest layers of the rete. The neoplastic tissue was well circumscribed, being separated on its lower border from the normal corium by a dense round-celled infiltrate.

We probably have here to do with a pigmented nevus, which, after remaining dormant for many years, began, for reasons quite unknown to us, to undergo malignant transformation. Until a quite recent period most of the malignant growths arising from pigmented nevi were described as pigmented alveolar sarcomata of the skin; but the studies of Unna and others have shown that most, if not all, of these growths are of epithelial origin, and should, therefore, be classed among the epitheliomata. They present many interesting features, differing in their structure from the ordinary form of epithelioma. Their alveolar arrangement is in marked contrast with the long finger-like or branching processes growing down into the corium characteristic of the latter neoplasm; their cells have lost their polygonal shape and their prickles, and many of them are filled with pigment. These growths are usually much more malignant than the non-pigmented variety, recurrences taking place with fatal persistency, and metastases are common and often wide-spread. *April 11, 1901.*

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### Peculiar Degeneration of the Epidermis in an Ulcer of Traumatic Origin.

M. B. HARTZELL, M.D.

W. G., about fifty years of age, a carpenter by occupation, struck the left thumb, at the root of the nail, an accidental blow with a hammer. This injury was followed by an abscess and loss of the nail, but complete healing followed within a reasonable time. Two months later the same thumb was knocked against the end of a wooden box, producing a superficial abrasion at the root of the nail. At the place of this latter injury a small ulcer, about one-fourth inch in diameter, formed, which obstinately refused to heal under any treatment, and at the end of six months' futile endeavor to heal it, it was excised under cocaine anesthesia. Cicatrization proceeded very slowly, but was complete at the end of a month. Upon microscopic examination of the excised tissue it was found that the epidermis had undergone a remarkable alteration. The interpapillary processes were greatly enlarged in



*a.* Areas of degenerated epithelial cells in the interpapillary projections of the retinal mucosum.



length and breadth, and the epithelium in the central portion of many of them had completely disappeared, forming cyst-like cavities containing a small quantity of granular débris. About the margin of these cavities were several rows of cells from which every trace of internal structure had vanished, nothing being left but the cell membrane. In places a few large round unstained cells without nuclei were to be seen, filled with numerous, faintly-defined, round, granular bodies bearing some resemblance to large spores. The papillæ of the corium showed a moderate round-celled infiltrate. No micro-organisms except a few staphylococci were found.

*April 11, 1901.*

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**A Demonstration of the Shrinking of Bloodvessels that Occurs as They are Ordinarily Prepared for Microscopic Examination, and of the Distortion of the Tissues which is Caused by this Shrinkage: Also the Exhibition of New Bloodvessels in the Inner Layers of Diseased Veins.**

ARTHUR V. MEIGS, M.D.

Everyone who has prepared sections of bloodvessels and has then examined them with the microscope must have been struck, as I have been, by the shrinkage that invariably occurs. It has seemed to me that bloodvessels prepared by any of the methods now in common use are reduced about one-third in size by the time they have been passed through the various reagents that are used before sections are finally cut and mounted on slides. For a long time I tried to devise a method by which this imperfection of preparation might be overcome, and at last it struck me that by placing glass tubes or rods in bloodvessels as soon as possible after death and never removing them until the tissue was ready to be cut the end might be partially attained. I have had such sections made for me by Dr. Robert Formad. The sections were prepared by the paraffin method. Glass rods or tubes were placed in the vessels at the time the postmortem examination was made, the tissue was stained in bulk, and the glass was never removed

until after the embedding was completed and the tissue was ready to be cut. When the vessels with glass rods or tubes within them were in course of preparation other pieces of the same vessels without any glass in them to prevent shrinkage were carried at the same time through the same reagents. Sections of the shrunken vessels and of those in which shrinkage had been prevented were mounted side by side, and my preparations show that the shrinkage amounts to about one-third of the total bulk. This shrinking greatly changes the appearances and relations of parts of the tissue, as might be expected. The sections seem to me absolutely to demonstrate the correctness of the opinion long held by histologists that the plicated membrane is quite straight during life, the plications being due to post-mortem contraction, which naturally throws the rigid fibrous membrane into folds. A study of this so-called plicated membrane shows it folded as usual in the shrunken sections while in those which were prepared with glass in them to prevent shrinking the membrane is everywhere much more nearly straight and in places entirely without folds. The appearance of the long narrow nuclei of the muscular tissue presents a great contrast in the two sets of sections. In those prepared in the usual way the nuclei are twisted upon themselves and are irregularly placed in the sweeping uneven circle formed by the muscularis. The result of this is to produce a general effect that is best described as a resemblance to basket-work, and this is the common appearance of the muscularis of bloodvessels when it is examined under the microscope with any moderate amplification. In the sections prepared in such a way as to prevent shrinkage there is a great contrast of appearance. The muscle nuclei are comparatively little twisted and they are nearly parallel with one another. This almost entirely takes away the basket-work appearance which is so distinct in the shrunken sections.

The other point of interest presented by the sections is the presence of new bloodvessels in the deeper layers of the wall of a diseased vein. The femoral vein is greatly and irregularly thickened by disease. The circular muscular layer is torn apart by the growth of fibrous tissue in it, producing an appearance similar to that of a vein which I described in a paper entitled "Endophlebitis," which I read before this society about a year

ago. In the sections of a femoral vein which I now show the diseased muscular tissue contains many new bloodvessels. This tissue is in many respects similar to that of embryos, and the appearance of the bloodvessels confirms me still more in the opinion I expressed several years ago in my book on the *Origin of Disease*, that bloodvessels often grow in diseased tissues in the same manner as they are so well known to grow in embryos independently, and are afterward joined to the older vessels. I do not believe that bloodvessels grow in diseased tissues in adults only by the process of budding, which is by offshoots from pre-existing bloodvessels, as has been taught by some pathologists. The sections that are now exhibited do not prove this statement, although they seem to me to add confirmation to the demonstration that I made by some of the illustrations in my book which has been mentioned.

March 28, 1901.

#### A Case of Intussusception of the Vermiform Appendix and Cecum, with Recovery and Subsequent Passage of the Invaginated Tissues by the Rectum.

JOSEPH MCFARLAND, M.D.

I am permitted to exhibit this interesting and remarkable specimen through the kindness of Dr. D. J. McCaa, of Ephrata, Penna.

The patient was a little girl, aged eight years, who suffered from an abdominal trouble which was diagnosticated intussusception. The condition was not thought suitable for operation and the case was treated tentatively.

The symptoms relieved themselves spontaneously, and during convalescence a mass of tissue was passed per rectum, and a rapid and uninterrupted recovery followed.

The discharged tissue mass consisted of two separate fragments, one of which was about 5 centimeters in length and 3 centimeters in breadth, ragged in outline and of a thinness about like that of the cecum. The tissue was so softened and macerated that it was not suitable for microscopic examination. The second fragment consisted of a flat piece of intestine (?), about the size of a half-

dollar, from which a tube about 10 centimeters in length, closely resembling the appendix vermiformis, was given off. It was extremely necrotic and soft. A segment was cut from its center and microscopic sections cut from it with the confirmation of the naked-eye appearance. The object certainly was the vermiform appendix. The organ was not inverted.

The condition seems to have been one of invagination of the vermiform and part of the cecum, the formation of adhesions, and the subsequent separation of the invaginated portion.

While the ileum frequently invaginates into the cecum, and this part of the intestine is the most frequent seat of intussusception, it is rarely that the cecum and vermiform appendix invaginate, and certainly quite unusual for subsequent recovery with discharge of the invaginated portion to occur.

*February 28, 1901.*

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### Carcinoma of the Pleura Diagnosed by Tissue Removed in Tapping.

J. D. STEELE, M.D.,

AND

J. H. GIRVIN, M.D.

*(From the Clinical Laboratory of the Presbyterian Hospital.)*

The patient is a white woman, aged fifty years, who was healthy up to three years ago, when she had an attack of pleurisy on the right side, which lasted for ten days and from which she entirely recovered. As long as she can remember there have been a couple of tumor-like masses in her right mammary gland. A year ago these began to grow rapidly larger, and this was soon followed by enlargement of several of the axillary glands. The mammary tumor is now somewhat ulcerated, the nipple is contracted, the whole gland is infiltrated, and there are two small tumors as large as walnuts in the axilla. She has never had rheumatism, and up to the commencing of the present illness has never suffered from heart trouble. Upon admission to the hospital examination showed absolute dulness and absence of vocal fremitus and breath



sounds, anteriorly from the second rib downward; posteriorly from the second dorsal vertebra downward, except that distant bronchial breathing is present over the area of dulness. Anteriorly to the left of the tumor and between it and the sternum is an area of distinct bronchial breathing. The motion on this side is absent. The apex beat of the heart is in the fifth interspace on the anterior axillary line. At the apex there is a very short systolic murmur, which is not transmitted and comes and goes. This was considered to be probably functional. The second pulmonic sound is much accentuated. The right border of the heart dulness merges into the dulness of the right chest. The examination of the left chest shows that it is practically normal except that some compensatory emphysema is present.

A diagnosis of right-sided pleural effusion was made. The chest was tapped in the ninth interspace in the posterior axillary line and twenty-seven ounces of a cloudy, blood-stained fluid were withdrawn. The specific gravity of the fluid was 1020; on boiling it became solid with coagulated albumin, and many red blood cells were found in the microscopic examination. Just before the needle was withdrawn a piece of tissue came through it with the fluid from the pleural cavity; this was 10 mm. in length and 2 mm. broad.

After tapping, the dyspnea, which had been intense up to that time, was greatly relieved. Examination of the chest after the removal of the fluid showed anteriorly resonance in the first and second interspaces, with complete dulness, absence of vocal fremitus and breath sounds in the area bounded by the second rib above, the anterior axillary line on the outer side, and the right edge of the sternum on the inner side. The lower edge of the liver is palpable at the left of the umbilicus. Its surface, however, seems to be smooth and no masses can be felt. Posteriorly resonance, breath sounds, and fremitus have partially returned down to the level of the puncture. The fact that after tapping the dyspnea was so greatly relieved and the heart returned to its normal position renders it probable that almost if not quite all of the fluid was removed and that the area of dulness in front is not due to the presence of a sacculated pleural effusion. The physical signs evidently point to a considerable thickening of the pleura. The

examination of the piece of tissue removed by the aspirator throws important light upon the nature of this thickening. It was embedded, cut, and stained with hematoxylin and eosin. The sections show that the tissue consists of nests of epithelial cells connected by a delicate fibrous tissue stroma. In some places the nests and masses of cells are broken apart by areas of hemorrhage. The cells are evidently epithelial in origin. The stroma is not great in amount, but can be plainly seen in the places that are not much distorted or broken apart. The diagnosis of carcinoma of the pleura and probably of the lung seems justifiable.

The progress of the case since it was first tapped has confirmed this diagnosis.

The patient is rapidly becoming cachectic. There has been great loss of flesh and strength. The fluid rapidly reformed and tapping has been twice resorted to, and in each instance about seventeen ounces of a fluid similar in character to that obtained at the first tapping has been removed. The blood count shows 14,000 leukocytes. The mammary tumor much resembles carcinoma in its macroscopic appearance, and the great thickening of the pleura, the rapid loss of flesh and strength, the rapid formation of an effusion of high specific gravity, and which contains blood, renders the diagnosis of malignant disease of the pleura a very probable one. This diagnosis is apparently confirmed and the character of the growth determined as carcinoma by the examination of the piece of tissue that we were fortunate enough to obtain while aspiration was being performed. The loosening of the fragment from the chest wall must be considered a fortunate accident, and one that cannot be depended on in determining the etiology of such pleural effusions.

The ease with which the diagnosis has been made in the present instance has seemed to render the case of sufficient interest to warrant the presentation of this report.

*February 14, 1901.*

## A New Method of Staining Elastic Tissue.

H. F. HARRIS, M.D.

As a result of a series of accidents I recently discovered the fact that hematein solutions, when prepared in a certain way, have a remarkable affinity for elastin, and that this substance may be differentiated clearly from other tissues by the employment of the peculiar stain in question; and inasmuch as the results obtained by its use appear to be in some particulars superior to those gotten by Weigert's method in my work the former has been recently usually substituted for the latter. The stain is made in the following manner: hematoxylin, 0.2 gm.; aluminium chloride, 0.1 gm.: 50 per cent. alcohol, 100 c.c. Dissolve the hematoxylin and aluminium chloride, and then carefully bring the solution to a boil; 0.6 gm. of mercuric acid is now slowly added, and as soon as the mixture assumes a dark purple color it is removed from the flame and cooled rapidly. The stain is filtered, and one drop of hydrochloric acid is added. A short time after cooling a flocculent precipitate is sometimes formed in the solution; this is immediately dissolved upon the addition of the hydrochloric acid. The stain should then be set aside for some weeks, as it will not, as a rule, give satisfactory results at once. I have not been able to find the reason for this, but the change does not appear to depend upon the continued absorption of oxygen by the hematein, for the reason that no degree of artificial oxidation seems to quicken the result. It must be admitted that the stain is somewhat capricious in its "ripening," but after this has been once accomplished it appears to keep indefinitely. The staining solution is used by immersing thin sections of tissue in it for from five to ten minutes, and the tissue is then washed for about a minute in a 1 per cent. solution of nitric acid in alcohol; the acid alcohol is then thoroughly removed with pure alcohol, and the sections are cleared and mounted. On account of the close relation of this stain to Mayer's muchematein, I would suggest that it be called elashematein. It may be of interest in this connection to remark that when tissues are treated with Mayer's mucicarmine, and afterward with an alcoholic solution of nitric acid, any elastin that may be pres-

ent stains much more brilliantly than do the other structures, and this method, as a consequence, may be used for differentiating between them. With both of these stains mucin is always decidedly colored, but inasmuch as this substance is rarely found in those localities where elastic tissue occurs, and is morphologically entirely unlike it, there is no possibility of confusing them.

*April 11, 1901.*

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### Cyclopic Monster.

W. E. ROBERTSON, M.D.

This specimen is of interest on account of its rarity rather than from any practical deduction which may be drawn from it. Monstrosities represent the widest deviations from the normal development, the acme of anomalous development as it were. Malformations may be classified according to their genesis thus:<sup>1</sup>

1. Those due to perverted growth, either in the direction of increase or decrease. 2. Those resulting from defective union of embryonic parts. 3. Those produced by partial or total cleavage of embryonal cell masses. In the first case the impaired growth may be due to several causes influencing the entire organism, or the cause may be a local one, often mechanical, as pressure from without or within, resulting in circumscribed impairment of growth. Such is the case in the cyclopean monster. The pressure is said to be exerted by the amniotic hood. Ahlfeld, while not denying the above hypothesis, believes that some cases may be explained by a probable increase of intracranial pressure, resulting in rupture of the early cerebral vesicle somewhere about the fourth week.

Ackerman, Quicken, and others believe the condition to result from some deeply seated cause, which profoundly influences development. In support of their view they instance the frequent association of these defects, that is, the appearance in the same individual of two or more abnormalities. According to Dareste,<sup>2</sup> a cyclops results from an arrested development of the anterior cerebral vesicle, possibly due to anomalies in development of the

<sup>1</sup> Hirst and Piersol. "Monstrosities."

<sup>2</sup> Compt. rend. 94, 1882; also Ann. d'Oculistique, 1891, p. 171.

amnion, by which the latter exerted more or less pressure or traction on the anterior cerebral vesicle. Geoffrey Saint-Hilaire<sup>1</sup> describes a cyclops as a monstrosity in which the more or less imperfectly developed visual organs approach the median line and eventually fuse, in proportion to the degree of atrophy of the olfactory organs. Ahlfeld believes that there are successive grades of the deformity, varying from a mere narrowing of the face with poor nasal development to a very imperfect single orbital cavity, situated about the middle of the face, with or without rudiments of one or both eyes, and above a more or less rudimentary nose. Under Cyclocephalus, Cyclops, or Synopsia, as the condition is variously termed, are included :

1. Ethmocephalus—nose-headed. The olfactory organs are not completely atrophied, and the nose is represented by a sort of proboscis, provided with one or two imperfect nostrils. There are two eyes and two eye-sockets.

2. Cebrocephalus—monkey-headed. Interocular region narrow and quite flat. No nose or any trace of it. Two orbital cavities and two eyes present.

3. Rhinocephalus. Single orbital cavity, containing two eyes more or less fused, above it a proboscis representing the nose. The cyclops presented is a rhinocephalus, having a cylindrical proboscis provided with a very imperfect nostril. Immediately below this is a fused orbital chamber, containing rudimentary structures, apparently portions of two eyes. No other malformation is apparent.

4. Cyclocephalus. No vestige of a nose or proboscis. Complete fusion of orbital cavities and orbits.

5. Stomocephalus. In this variety the deformity is similar to that of the rhino or cyclocephalus, but, in addition, the lower part of the face is affected. The upper and lower maxillary bones are very defective, but the normal amount of integument is provided, so that the latter, being redundant, hangs in folds, especially in the region of the mouth. The monsters may present other deformities than those of head and face. Anencephalus is a rather frequently associated anomaly. Polydactylism is a frequent congener. A point of interest in connection with this case is the fact that the mother, when about three months pregnant, was operated upon

<sup>1</sup> Traites des Tumatologie. Paris, 1832-37.

for a fungous-looking tumor of the cervix, microscopically a squamous celled epithelioma. The cervix was amputated. The woman went along to term, and was then delivered of the monstrosity. There has been no return of the growth.

*April 11, 1900.*

### Nerve Fibers in the Pia of the Spinal Cord.<sup>1</sup>

(ABSTRACT.)

F. X. DERCUM, M.D.,

AND

WM. G. SPILLER, M.D.

In examining microscopic sections from a case of adiposis dolorosa we found many fine medullated nerve fibers within the pia covering the posterior columns of the spinal cord. Medullated nerve fibers within the spinal pia seem to be of very rare occurrence. Probably the first observation of this kind was made by Saxer. He was inclined to look upon these fibers as an attempt at regeneration of the spinal cord, but was very guarded in expressing such an opinion.

Fickler also has seen medullated nerve fibers in the spinal pia. He believed that they were newly formed fibers of the crossed pyramidal tract, and that in this round-about way a connection was made between this tract above the area of compression and the nerve cells below it. The improvement in the symptoms he explains as dependent upon these newly-formed fibers. The only reference Fickler gives to similar findings is to Saxer's case of syringomyelia mentioned above.

Nageotte observed medullated nerve fibers in the pia of the spinal cord. They were found in all parts of the periphery of the cord and deep in the anterior fissure, but were most numerous near the anterior roots, in which they seemed to arise; they were also found in the walls of the vessels of the pia. He gives no references to cases in the literature in which nerve fibers were found in the pia. He believes that in his cases they were newly formed fibers of the anterior roots.

<sup>1</sup> Published in full in the *Revue Neurologique*, March 15, 1901.

Saxer and Fickler do not speak of medullated nerve fibers within the pia covering the posterior columns, but the statements of Nageotte would seem to imply that he had found them in the posterior part of the pia, and yet in his cases they were more numerous near the emergence of the anterior roots. In our case they are numerous only in the posterior part of the pia, although an isolated fiber may occasionally be found in the pia over the lateral columns. There is no distinct degeneration of the posterior roots, and therefore it is not very clear why there should be any formation of new fibers. The columns of Goll in the cervical and upper thoracic regions were slightly degenerated and no cause for this degeneration could be found. The nerve fibers in the pia were very numerous in the sacral, lumbar, and lower thoracic regions, but were not detected in the cervical cord. We have attempted to determine the source of these fibers, and with this object in view have made many transverse and longitudinal sections from areas where the nerve fibers within the pia were very numerous, and have even made unbroken serial sections of some parts. These nerve fibers have a very irregular course and it is impossible to trace them even in serial sections. They are so matted together that we cannot with certainty determine their continuation in successive sections. After many attempts we succeeded in obtaining a section in which a few medullated nerve fibers were seen passing through the pia and toward the posterior columns. It seems most probable that the nerve fibers within the posterior pia come from the posterior roots, and ascend a considerable distance within the pia before entering the posterior columns. The relatively long course of these fibers, if our view is correct, would explain the difficulty of obtaining sections in which the nerve fibers are seen passing from the pia into the spinal cord. It is not improbable that the nerve fibers enter the cord in small bundles and therefore it might be largely a matter of chance whether or not a section were obtained showing these fibers at their point of entrance into the cord. It is also possible that these nerve fibers lose their myelin sheaths in entering the cord, in the same manner as do the posterior roots.

The nerve fibers within the pia over the posterior columns were fine and had usually a longitudinal course, but some transverse

fibers were also found, especially about the bloodvessels, where the nerve fibers were very numerous. These nerve fibers within the pia were not only medullated, but from the presence of elongated nuclei along their edges probably were covered with a sheath of Schwann.

As the posterior roots in our preparations do not appear to be degenerated, it is difficult to explain the existence of the nerve fibers within the pia over the posterior columns as an attempt at restoration of posterior root fibers. There seems to be no reason why nerve fibers in our case should grow out into the pia in the manner supposed by the writers quoted above, and there is another possibility that occurs to us and deserves mention. It is probable that non-medullated nerve fibers exist normally in the spinal pia and are not detected because they have no medullary sheaths. The posterior roots lose their medullary sheaths in passing through the pia into the cord, and if nerve fibers from these roots ascend in the pia it is not unreasonable to suppose that they may remain unmedullated. Occasionally, however, they might be medullated, just as are occasionally the nerve fibers of the optic nerve within the eye, and if this occurred they would easily be detected. This, however, is merely offered as a hypothesis.

*April 11, 1901.*



# Proceedings

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#### Some Remarks upon Venom and Antivenene.

JOSEPH McFARLAND, M.D.

Our knowledge of venoms and their effects has passed through three distinct stages in its evolution. In the first, attention was directed to the snakes, their venom apparatus, and the chemical investigation of the venom itself. The second was characterized by careful study of the physiologic action of the venom upon the lower animals, and began about the time that experimental physiology had its inception. The third epoch began with the recent discovery of the phenomena of immunity, immunization, and the therapeutic employment of the antitoxic serums.

Each period has a literature peculiar to itself, with some overlapping, and during all three periods there has been a more or less earnest search after antidotes and cures for snakebites.

It is to some facts that have been determined during the third period that I desire to call your attention this evening.

The occurrence of immunity to serpents' venom seems to have been suspected for many years, but the first to determine its occurrence by experiment seems to have been Sewall, of the University of Michigan, who published in the *Journal of Physiology*, 1887,

vol. viii., p. 203, a paper upon venom, in which he records his success in immunizing pigeons to rattlesnake venom.

The paper seems to have attracted very little attention, and the matter was permitted to rest until Phisalix and Bertrand took it up after interest in immunity and immunization had become general. Their paper appears in the *Compte Rendu de l'Acad. des Sciences de Paris*, 1894, vol. cxviii., p. 288.

This paper was followed by another, *Compte Rendu de l'Acad. des Sciences de Paris*, February 5, 1894, t. cxviii., p. 356, and *Compte Rendu de la Société de Biologie de Paris*, February 10, 1894, 10th series, vol. i., p. 111, in which it was further shown that when guinea-pigs were immunized by venom, a protective (presumably antitoxic) substance appeared in their blood.

The subject of immunization and the formation in the immunized animals of antitoxin (*antivenene*) was greatly elaborated at the hands of Calmette, whose papers in the *Annales de l'Inst. Pasteur*, 1894, vol. viii., p. 275, and vol. ix., p. 225, deserve careful reading, and cover the subject in a most complete manner.

Close upon Calmette came Fraser, of Edinburgh, who, on May 15th, 1895, showed before the Medico-Chirurgical Society of Edinburgh a rabbit immunized to cobra venom to the extent of fifty times the minimum fatal dose, and whose blood serum was protective for other rabbits in doses of  $\frac{1}{250}$  of a cubic centimeter.

In the following year Fraser published two large contributions upon the subject (*British Medical Journal*, June 15, 1895, vol. i., p. 1309, and August 17th, vol. ii., p. 416). Our knowledge of the subject as the results of these and foregoing researches may be briefly summarized as follows:

Serpents of certain families are provided with a poison apparatus consisting of a venom (modified parotid) gland, and a fang, or perforated tooth, by which the poison is injected.

The poison is a clear, yellowish fluid, with an acrid odor in some cases, and a slightly oily feel. It is highly irritating when applied to the mucous membranes. It dries readily in the form of scales, which fracture in drying, and readily separate from the polished surface of the dish. Scarcely any of the virulence of the venom is lost by drying.

The activity of the venom depends upon the proteid substances which it contains. One of these can be destroyed by heating to about 80° C. for one-half hour, the other resists 100° C. for some minutes. The different venoms contain different proportions of these principles, and it is probable that the variation in physiologic effects observed depend upon these proportions.

The precipitable principle is thought by most writers to be a *globulin*. Upon its presence the local irritative and neutralizing effects of the venom depend. Venoms such as those of the vipers contain relatively much of this globulin. The other principle which is not easily precipitable is probably an *albumose* (Mitchell and Reichert regarded it as a peptone).

Its chief activity is upon the nervous system, and it is the lethal element of the venom.

The physiologic action of the venom has been fully investigated regarding its action upon the blood, the heart, and the respiration. It causes rapid coagulation of the *blood* when thrown into the circulation in large quantities, so that the animal dies at once; the heart and great vessels are found full of black clots. If the dose is smaller, so that the animal lives for some time, then dies, the blood is black and fluid. If very small doses are given the blood loses some of its coagulability.

Upon the *heart* the venom has but a slight depressing action.

Upon the *respiration* the venom acts profoundly, always causing death by paralytic asphyxia, depending upon the action of the venom upon the respiratory center.

Certain animals, particularly the mongoose, possess a certain degree of natural immunity to venom.

Susceptible animals can be immunized to venom by the usual method of progressive administration, and little difficulty is experienced in increasing this immunity to 50–100 fatal doses.

In the blood of the animals in which this high degree of forced immunity exists, *antivenene*, a substance protective for other animals when injected into them, makes its appearance. This protection is manifested when the antivenene is given before, mixed with, or subsequent to a minimal fatal dose of venom.

The antivenene is useful for therapeutic purposes, and its value can be accurately calculated and expressed as units, and the neces-

sary dose of a serum of proper strength need not exceed twenty cubic centimeters.

The antivenene prepared by immunizing animals to cobra venom operates actively upon the venoms of all known venomous serpents, as well as scorpions, spiders, and some insects.

It is antagonistic to the respiratory or nervous poison, slightly so to the irritative globulin contained in the serum.

The original experiments which I desire briefly to record here were made during 1899 and 1900 upon three horses placed at my disposal through the kindness of H. K. Mulford Co.

The venoms used were almost exclusively those of rattlesnakes furnished by the same firm. Some cobra venoms with which I made some experiments was very kindly sent me from France by Prof. Calmette.

I began my research upon the same plan as Calmette had outlined, and gave my horses some preliminary injections of the cobra venom. Upon consideration, however, it occurred to me that in all probability the serum which I would prepare would be called upon to counteract the effects of crotalus venom, and that it should, if possible, afford protection against the irritative globulins of the crotalus venom. It seemed logical to conclude that serums prepared by the injection into animals of cobra venom which contains some of the irritative globulins, or of heated venoms from which this globulin was all precipitated, would, other things being equal, yield an antivenene active against the nervous poison, and potent to save life, but not potent to prevent the destruction of tissue by the globulins. These thoughts led me to modify the method of immunization, so that I abandoned the cobra venom and subsequently employed crotalus venom only. As the local effects of the venom are so extremely severe, I modified the venom in the beginning by heating it so as to precipitate the globulins, then filtering it. After a period of rapid immunization to the heated venom, which, of course, could only be expected to afford immunity to the nervous poison, a second mode of operation was begun. Dilute solutions of unheated venom were now given subcutaneously. Very small doses were administered at first, but it at once became evident that, while some immunity had been established to the nervous poison, no immunity had

been established to the irritative poison, as each animal immediately after the injection of the venom suffered from a hemorrhagic edema, which sometimes assumed dangerous proportions and led to extensive suppurations and tissue exfoliations. In spite of what was thought to be moderate administration of the venom, two of the horses succumbed to the extremely severe local effects. The impossibility of overcoming these local effects suggested to me that a third modification of the treatment might be brought about, and that by intravenous injection of dilute watery solutions of the venom its further dilution in the circulating blood might enable the animal to tolerate it and lose the local effects. This proved to be the case, and a third period succeeded, during which the remaining horse received diluted crotalus poison, in increasing and then varying doses, into the vein.

To sum up, the treatment of the animal consisted of:

1. The injection of heated cobra venom beneath the skin.
2. The injection of heated crotalus venom beneath the skin.
3. The injection of unheated crotalus venom beneath the skin.
4. The injection of unheated crotalus venom into a vein.

The immunity attained by the horse was highest during the second period, during which it received as much as 3 *grams of the dried venom* at a dose. Of the immunity to the irritative globulin which the animal received during the third period less gratifying results can be reported. The largest quantity given at a dose was 1 gram of the dry venom under the skin, and it almost killed the animal by the enormous slough it occasioned. The recovery was followed by no immunity, as 0.25 gram given later caused a similar edema and slough.

The last period was most successful. The intravenous injection of the unheated venom was conducted with great caution, and I was able to ascend from 0.1 gram to 0.75 gram. The horse, however, always showed a marked and extremely interesting physiologic effect from the venom injections, and when they were increased would fall unconscious for some minutes, then gradually regain consciousness and strength again, some hours elapsing before it was apparently well and ready to eat. The horse fell so suddenly, as the effects of the venom were manifested, that we were obliged to sling him to prevent injury. These phe-

nomena probably depended upon the globulin, as the immunity to the nervous poison was marked, and not enough was contained in the administered venom to injure the animal.

Notwithstanding the fact that these intravenous injections numbered ten, and continued from February to October, 1900, the horse acquired *no immunity* worth mentioning to the irritative globulins, as is fully illustrated by the manner of his death. On October 16, 1900, he received 0.5 gram of the dried, unheated venom into the jugular vein. Through an accident a part (presumably about one-fourth) of the injected fluid entered the subcutaneous tissue near the vein. The result was an edematous swelling of the whole anterior portion of the neck and the development of symptoms of suffocation. Tracheotomy was performed, but the local conditions became so bad that it was impossible to save the animal, and it died.

The horse was bled four times and its serum tested for the presence of antivenene. Unfortunately no bleeding was taken at the end of the time during which heated venom only was used. I think it was probably toward the end of that time that the serum would have been strongest in its protection against the nervous poison.

The first bleeding was taken after the first intravenous injection, and the serum was found to afford an uncertain amount of protection against the lethal dose of venom.

The second bleeding was taken after four intravenous injections, and was found to perfectly protect against the least dose of venom that was fatal in about one-half hour upon intravenous injection, the dose of serum necessary to accomplish this being 1 c.c. It was also found that this serum also afforded very nearly the same amount of protection to the cobra venom sent me by Calmette.

The serum of the third bleeding as well as that of the fourth bleeding failed to protect satisfactorily against cobra venom, so that it had probably declined in strength.

The results of the investigation may be summarized as follows:

1. By the subcutaneous and intravenous injection of unheated crotalus venom it is possible to immunize horses to the chief toxic element—the nervous poison.
2. The immunity thus afforded is very slightly protective

against the irritative poison contained in the venom, and animals whose serum contains much antivenene may succumb to its local effects.

3. The development of the immunity is accompanied by the occurrence of large quantities of antivenene in the blood of the immunized animal.

4. The antivenene is fully able to save animals from both cro-talus and cobra venoms.

5. The quantity of antivenene in the blood fluctuates according to circumstances, as do other antitoxic serums, and declines as the vital condition of the horse is depressed.

6. The normal endurance of horses to venoms varies considerably, as does their resistance to diphtheria and tetanus toxins, so that only one out of three horses survived treatment for a considerable length of time.

7. The intravenous method of administering the unmodified venom is by far the best, as it is not attended with sloughing of the tissues. Great care must, however, be exercised in order that the venom does not accidentally enter the subcutaneous tissues.

8. As the immunity does not extend to the irritative poison, and as the protection afforded to animals receiving antivenene is against the venoms, not the irritative poison, it is probable that Calmette's method of immunizing animals with modified (heated) venom, which contains none of the irritative substance, is greatly to be preferred, as causing the animals less suffering and not endangering their lives.

*April 25, 1901.*

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#### Diphtheria Bacilli in Noma.\*

JOSEPH WALSH, M.D.

Led on by the discovery of Freymuth and Petruschky<sup>1</sup> of diphtheria bacilli in two cases of noma, I examined eight cases of the disease that fell under my observation for the same organism. These cases occurred over a period of two years and a half at St.

\* The investigations were carried out in the Pepper Clinical Laboratory. It was through the kindness of Dr. Bryan that I obtained the cases.

Vincent's Home. All of these eight cases showed in cultures the true diphtheria bacillus—that is, the true diphtheria bacillus as measured by the criteria of today. For my differentiation of it from others, and the pseudodiphtheria bacillus, I followed Sternberg as to its growth on different media, and Neisser and others in its staining qualities. Each organism was proven also by inoculation into guinea-pigs or (in one case) a rabbit. The amount inoculated was routinely small, and was taken from a growth on Loeffler's blood serum. Only one of the eight cases showed a pure culture of diphtheria organisms, that the second one was in association with diphtheria. The others showed, beside very large bacilli, diplococci, etc., though I paid attention only to the diphtheria bacilli.

The cases were as follows :

CASE I.—(November 2, 1898.) Helen C., aged three and a half years; mother died of Bright's disease; the child had an acute attack of the same disease at the age of two and a quarter years. On June 28, 1898, she developed diphtheria, and was sent from home to the Municipal Hospital. She returned exactly two months later (August 28th) and the throat still looked diphtheritic, though the cultures were negative. October 27th, two months later, she developed measles, and a day or two later began to whoop. She was at this time in the isolation ward with two other children suffering likewise with measles. One of these two developed what appeared, clinically, to be diphtheria. This one was given 1000 units of antitoxin, and Helen and the third one 500 units each as a prophylactic. Cultures from this case to the Board of Health were negative; my cultures of the same case showed a streptococcus. Two days after the injection of the antitoxin (November 2d) a gangrenous patch was noticed on the interior of Helen's cheek. On November 5th, the day after it was first noticed, the patch was cultured, and it was cultured again on the 7th. Both cultures showed true diphtheria bacilli that killed guinea-pigs in twenty-four to thirty-six hours, the organisms being recovered from the blood and organs in both cases. On account of this finding, on November 9th she was injected with 1500 units of antitoxin, though her condition was very low. November 12th she died. The gangrenous patch, which was in the middle of the



left cheek, measured about one inch in diameter, and extended through all the tissues from the interior outward. The upper alveolus on the left side was entirely necrosed, and there was a perforation through to the nose. Smears from the patch showed with Loeffler's methylene-blue faintly staining bacilli in long threads, small bacilli resembling in general appearance diphtheria bacilli, small and large diplococci, and very large bacilli. Smears stained with Gram's showed very large bacilli and small bacilli and diplococci that were difficult at times to differentiate. A section of the diseased tissue bordering on the healthy, taken after death, showed with Loeffler's methylene-blue many large bacilli and numerous chains of small bacilli, the chains being slightly curved; with Gram's only large bacilli and small diplococci. I carried my isolation attempts no further than the diphtheria bacilli.

CASE II.—(February 6, 1899.) John O'N., aged two and a half years. Well nourished. January 31st he developed pharyngeal diphtheria, two days later noma. The noma appeared on the left upper alveolus, destroyed the gums about two teeth (canine and molar), and perforated through to the nose. Cultures from the pharynx on January 31st showed diphtheria bacilli. The noma patch was cultured first on February 6th, when a pure culture of diphtheria bacilli was found. The child gradually improved, and neither from the pharynx nor the noma patch were diphtheria bacilli found after February 15th. By March 8th the child was almost entirely well. In this case the guinea-pig injected died in about eighteen hours, and I failed to recover the organisms, yet there seemed to be no doubt as to the diagnosis. The guinea-pig was small, weighing 216 grams. The general picture found at the autopsy pointed to the diphtheria bacilli. A second culture from this case showed, beside diphtheria bacilli, very large bacilli which I isolated and injected into a guinea-pig without result.

CASE III.—(April 28, 1899.) Michael M., just over measles (epidemic) when the gangrene came on. It appeared associated with an ulcerative stomatitis almost simultaneously on the left cheek and left alveolar process. It gradually spread till all the teeth fell out, almost the entire alveolar processes sloughed off, with perforation of the palate into the nose, and the destruction of the whole left cheek, nose, and a part of the chin. The child lived four

weeks, and practically died of starvation. Cultured four times, on April 12th, 16th, 20th, and 28th; each time the diphtheria bacilli were found. Guinea-pigs were injected twice from cultures of the 12th and 28th.

CASE IV.—(April 28, 1899.) Hugh B., aged four and a half years. Just over measles (epidemic). The gangrene began at the margin of the teeth below lower incisors, in connection with ulcerative stomatitis, spread gradually till it implicated five central teeth and the gums in connection therewith. The alveolar process sloughed to its base. Recovery. Cultured on April 28th, and true diphtheria bacilli found.

CASE V.—(June 11, 1899.) Mary M., aged four years. Had measles immediately previously. The gangrene began below left anterior molar, destroyed all the left lower alveolar process from median line back. Recovery. Cultured June 11; true diphtheria bacilli found.

CASE VI.—(October 1, 1899.) James F., aged five years. Had measles during an epidemic two years before. September 14, 1899, developed diphtheria. Recovered from this, though it is not known if all diphtheria bacilli left his mouth. His digestive tract continued to show disturbances in the shape of a chronic diarrhea and an ulcerative stomatitis. On September 28th a gangrenous patch was noticed on the left upper alveolus. This necrosed almost into the nose, causing the loss of four teeth. Cultures were made on October 1st. They showed the true diphtheria bacillus, which inoculated into a rabbit (no guinea-pigs being at hand) killed it in three days. The bacilli were recovered. The child recovered.

CASE VII.—(January 20, 1900.) Sadie F., aged eighteen months. Teething. Not very well nourished, yet had no previous disease. For the last two weeks has had small hemorrhagic ulcers at the margin of the lower teeth. Yesterday the noma developed. During its progress the lower alveolus necrosed from the median line all the way back on the left side. The lower lip perforated just below the left angle of the mouth. Cultured three different times. Diphtheria bacilli found each time. Guinea-pigs injected twice and bacilli recovered. The bacilli reinjected once and recovered. Child died.

CASE VIII.—(May 21, 1900.) Joseph C., aged four years. The gangrene began at the upper part of the back tooth, spread up the alveolar process, attacked the cheek, perforated and spread over the face. When he died almost the whole face was eaten away, both alveolar processes, both cheeks, the entire nose, and the tissues about the left eye, leaving the eyeball bulging. Cultured May 21, 1900, showed true diphtheria bacilli.

Four of these cases began with an ulcerative stomatitis. This is by no means uncommon, as the text-books indicate (Cabot, in *American System of Practical Medicine*, 1898, and *Twentieth Century Practice of Medicine*). A number of cases, probably fifteen in all, of ulcerative stomatitis were cultured in the hope of finding diphtheria bacilli, but in vain.

The following are examples of such cases :

Fredie (April, 1899), aged three years. Had measles two years before, was suffering again from an attack of the same (I cannot vouch for their being both of the same variety, though the nurse assured me they were). Small hemorrhagic ulcers developed at the border of the lower teeth, and eventually a distinct ulceration of the right angle of the mouth. The cheek and mucous membrane about this ulcer became red and inflamed, gradually became hard and indurated, turned slightly purplish, and we thought we had a case of beginning gangrene. This inflammation continued several days, and gradually disappeared without any destruction. The ulcers at the angle of the mouth and those on the teeth were twice cultured without result as to diphtheria bacilli. Another such case was John P. (September 28, 1899), aged two and a half years. He manifested an ulcerative stomatitis that progressed in its destructiveness until several teeth were loosened and one cheek badly swollen, but no diphtheria bacilli were found on culture, nor did the disease advance to noma. The child gradually recovered.

At this time there were in one ward a number of cases of ulcerative stomatitis manifesting itself principally by ulcers on the gums around the teeth. Many of them were cultured. On one day five and another day four. In no case were diphtheria bacilli found, nor did any case subsequently develop noma.

Other cases of noma reported in the literature in which diphtheria bacilli were found are as follows :

Freymuth and Petruschky<sup>1</sup> two. The first a case of noma genitalium associated with diphtheria of the throat, following measles. The diphtheria and noma were both cured by injections of antitoxin. The second was a child of eight years, suffering from typhoid. The gangrene began on the alveolar process. This was also cured by injections of antitoxin. Bishop and Ryan<sup>2</sup> found in one case what was probably a pseudodiphtheria bacillus, but possibly a true diphtheria bacillus of weak virulence.

As to other investigators, omitting those who were led astray by the organisms of putrefaction and probably indifferent micro-organisms and those who made no cultural attempts or got only negative results, I will mention four who found organisms that seem to me possibly to have been causative agents.

Schimmelbusch<sup>3</sup> found in one case cocci, staphylococci, streptococci, and small bacilli. The last predominating, he carried them through a series of inoculation experiments without result; Foote<sup>4</sup> found in one case cultured only on agar, cocci, staphylococci, diplococci, and streptococci. Ranke<sup>5</sup> found streptococci, Guizzetti,<sup>8</sup> in one case, streptococci.

On account of the putrefaction going on in the tissues it is natural to expect that the organisms of putrefaction would be found in large numbers and in association with them numerous other saprophytes. Yet it is very probable that these organisms do not set up the process. Whenever we find moist gangrene, and noma is a typical example of it, we find the gangrene occurring secondarily to some other process, this other process being usually necrotic in character. The important agents then in the etiology of noma would not be the putrefactive organisms, but the organisms that set up the primary necrotic process. The organism that stands out pre-eminently in its power of causing necrosis is the diphtheria bacillus.

Moreover, it is a fact acknowledged by all specialists in children's diseases that diphtheria is especially frequent in association with and after measles. We never have an epidemic of measles at St. Vincent's without seeing some cases of it. If noma may be caused by the diphtheria bacillus, is it not natural that it should be seen especially after those cases when diphtheria itself is common? In a collection of 133 cases from the literature by Hilde-

brandt<sup>6</sup> and Perthes<sup>7</sup>, where the previous or associated disease was mentioned, noma occurred with or after measles in 53.

The cases in which streptococci were found I would attribute to them. Streptococci are not so frequent or so saprophytic that they should be found in many cases of gangrene without reason. In the further study of Hildebrandt and Perthes' collection of 133 cases we find noma associated with

Measles . . . . .	53 times.
Typhoid fever . . . . .	26 "
Chronic diarrhea . . . . .	21 "
Scrofula . . . . .	19 "
Smallpox . . . . .	9 "
Diphtheria and measles . . . . .	2 "
Diphtheria and typhoid . . . . .	1 time.
Diphtheria of the genitalia . . . . .	1 "
Diphtheria and scarlet fever . . . . .	1 "

In this list measles comes first, typhoid fever second. I have never seen a case following typhoid fever, yet remembering the capability of the typhoid organism for producing local necroses, I think it might be worth while culturing such a case for the typhoid bacillus itself if the diphtheria bacillus or the streptococcus were not manifest.

The two conditions that follow typhoid fever in frequency, namely, chronic diarrhea and scrofula, mean nothing except as regards the malnutrition of the patient. Then comes smallpox, a disease in which, too, local necroses are common.

It may be asked: "If due so frequently to diphtheria bacilli, why should it not be contagious, at least so far as the diphtheria is concerned?" I would answer that in my small experience I could not say it was not contagious.

As noma and diphtheria follow measles, noma and diphtheria are frequently associated at least at St. Vincent's. From June 1, 1900, to April 1, 1901, we had no case of diphtheria and likewise none of noma. Previous to that time the dates at which children were sent to the Municipal Hospital or died of diphtheria mark the dates of my noma cases.

Many attempts to produce noma by the inoculation of small pieces of diseased tissue into lower animals have failed completely, or have resulted only in the production of small abscesses.

Considered from the stand-point of this paper, this would be natural, since the causative microorganisms, even though still present, would be introduced into a healthy animal in company with large numbers of organisms of putrefaction that might easily destroy them or at least lessen their virulence.

CONCLUSIONS. 1. True diphtheria bacilli are found in connection with many noma cases. Since noma is a species of moist gangrene, requiring probably from analogy two different microorganisms, one a saprophyte to produce the putrefaction, another a parasite to produce the primary necrosis, it is possible that in these cases where diphtheria bacilli are found they may be the primary causative agents.

2. When other pathogenic microorganisms capable of producing necroses are found, it is possible that they may be the primary excitants.

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*May 9, 1901.*

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### The Histologic Changes in Diphtheria—A Lantern Slide Demonstration.

RICHARD M. PEARCE, M.D.

The lantern slides used in this demonstration were loaned by Dr. W. T. Councilman, under whose direction they were made, during the preparation of the work which is briefly summarized below.<sup>1</sup>

About sixty lantern slides, illustrating the development and structure of the membrane and the changes in the liver, spleen, kidney, lung, lymph nodes, heart, bone-marrow, and alimentary canal were exhibited.

<sup>1</sup> A Study of the Bacteriology and Pathology of Diphtheria. A Study of 220 Fatal Cases. W. T. Councilman, F. B. Mallory, R. M. Pearce. *Journal of the Boston Society of Medical Sciences*, vol. v., No. 5.

*Summary of Results of Histologic Examination.*

*Membrane.* Diphtheria bacilli are found usually in the necrotic tissue and in the exudation; never in the living tissue or in connection with the primary degenerative lesions of the epithelium. It seems probable that the primary lesions are due to a toxic substance produced by bacilli growing in the fluids of the mouth or throat. When necrosis or injury of the epithelium is produced by this toxic substance the tissue is then invaded by the bacilli. Other microorganisms, particularly the pyogenic cocci, are frequently found associated with the diphtheria bacilli. The first step in the production of the false membrane is degeneration or necrosis of the epithelium, often preceded by direct division of the nuclei of the epithelial cells. An inflammatory exudate, rich in fibrin, coming into contact with this epithelium forms a definite fibrin network. Associated with this, especially on epithelial surfaces having several layers of cells, a hyaline membrane is also frequently formed. This hyaline membrane may be formed from the fusion of the protoplasm of the cells undergoing hyaline degeneration, the nuclei of the cells disappearing and leaving spaces which give the membrane a reticular appearance. This hyaline membrane may also be formed by a hyaline degeneration of exudation cells. The most typical membrane is found in the larynx and trachea. The membrane never forms on intact epithelium, but may extend over it. In the connective tissues and blood-vessels beneath the membrane a hyaline fibrinoid degeneration may occur. Degeneration of the mucous glands is pronounced.

*Heart.* Fatty degeneration of the muscular fibers was found in forty-six of sixty-seven cases examined. It was most marked in the vicinity of the endocardium. In cases of great severity, dying shortly after entering the hospital, this degeneration was the only lesion of the myocardium. Segmentation and fragmentation of the myocardium was not observed. In thirteen cases very extensive degeneration leading to complete destruction of the muscle fibers was found. This consisted of a fatty degeneration with disappearance of the contractile elements. The sarcous elements disappeared, their place being taken by a granular material, with the formation of large, irregular vacuoles, which could be readily dis-

tinguished from those of fatty degeneration by their size and irregularity.

A further form of degeneration consisted of a complete destruction of the fibrillæ, with the formation of large, irregular hyaline masses. This was found only in the later stages of the disease, the average duration being about fifteen days. It was always more marked near the endocardium. Various degenerative changes of the nuclei of the muscle fibers were noted.

Interstitial lesions occurred in two forms. First, in six cases an acute interstitial myocarditis, characterized by a large number of plasma cells between the muscle fibers, was found. Lymphoid cells were occasionally seen, but polymorphonuclear leukocytes were rare. This condition may or may not be accompanied by degeneration of the muscle fibers. The accumulations were sometimes circumscribed and sometimes diffuse. This condition is analogous to the acute interstitial, non-suppurative nephritis of the kidney. The average duration of this condition was ten days. The second form of myocarditis was more chronic in its character and evidently secondary to degeneration. The interstitial tissue was swollen and infiltrated with large cells of an endothelial character, with considerable formation, in some cases, of connective tissue. The average duration of this condition was seventeen days.

Heart thrombi were found in eight cases. There seems to be some relation between thrombi and the acute interstitial changes of the heart muscle. In seven of these eight cases acute interstitial myocarditis was found.

*Lungs.* Bronchopneumonia was present in 131 cases, of which in 76 it was discrete and in 55 confluent. The process begins as an infection of the atria, and from there extends; it may be limited to a single acini, to lobules, or to groups of lobules. To the condition in which only single acini are involved, which is essentially the primary lesion, the writers have given the name "acinous pneumonia," to distinguish it from the condition in which the entire lobule is involved. There is little lateral extension of the infection through the walls of the alveoli. Inflammation of the terminal bronchi is also present, but not necessarily of the larger bronchi. Small areas of atelectasis and emphysema were frequently found. Acute lobar pneumonia did not occur in any of



these cases. Inflammatory edema was common, but a general edema of the lungs comparable to the circulatory edema of adults did not occur.

The character of the exudation varies greatly; it may be fibrinous, hemorrhagic, serous, or almost entirely cellular. The cells of the exudation are mainly leukocytes and in part cells derived from proliferation of the lining epithelium. Lymphoid and plasma cells are found not only in the exudation but in many cases infiltrating the interstitial tissue. Necrosis leading to abscess was not an uncommon feature. Dilatation of the lymphatics was very common. No definite relation could be demonstrated between the character of the exudate and the infecting microorganisms. Pneumococci, streptococci, and diphtheria bacilli were found in connection with serous, purulent, fibrinous, and hemorrhagic exudates and with necrosis and abscess formation. Diphtheria bacilli were very frequently found, and may be the cause, without the aid of other microorganisms, of bronchopneumonia, necrosis, and abscess formation.

*Spleen.* The most obvious lesions of the spleen consisted of the formation of foci of epithelioid cells in the lymph nodes. These epithelioid cells are phagocytic, and the nuclear detritus found in the foci comes generally from the lymphoid cells, which are engulfed and destroyed by the phagocytic cells. Large numbers of plasma cells are found throughout the pulp of the spleen. In the veins an accumulation of lymphoid cells was occasionally found beneath the endothelium of the intima.

*Alimentary Canal.* In the stomach and intestines, aside from an occasional extension of the membrane, the only important change is the hyperplasia of the lymph nodes with a proliferation of the endothelial cells.

*Liver.* Lesions of the liver in diphtheria are not characteristic, and do not differ from those found in other infectious diseases; they are due to the action of soluble toxic substances and not to the direct action of the diphtheria bacillus. The most common lesions are fatty and granular degeneration of the liver cells with necroses, which are found chiefly in the centers of the lobules. A slight hyaline degeneration of the capillary walls is seen occasionally, as is also a proliferation of the endothelium.

*Kidneys.* *Degenerative* changes were found in 112 cases, being chiefly cloudy swelling, fatty degeneration, and hyaline degeneration. Hyaline degeneration was found very commonly and was most marked in the proximal convoluted tubules. *Acute interstitial non-suppurative* nephritis was found in 43 cases. The infiltration was made up chiefly of plasma cells with numerous lymphoid cells and a few polymorphonuclear leukocytes, and occasionally phagocytic and endothelial cells. Various cells were observed which seemed to indicate stages of transition between the lymphoid and plasma cells. The accumulations of cells were generally focal, and were most numerous at the base of cortex adjoining the pyramids, just beneath the capsule, and around the glomeruli. Degenerative changes of the tubules generally accompanied this infiltration, but were not constant. In many of these cases large numbers of the infiltrating cells were found in the bloodvessels. They frequently showed mitotic figures, but not so frequently as did those outside the vessels. Omitting three cases, in which death occurred after the forty-second day, the average duration of the cases in which this condition occurred was sixteen days. In the cases in which the lesion was most marked the average age was eleven and a half days. In younger children infiltration was less marked. *Glomerulonephritis* was found in eleven cases, in nine of which the chief lesion was a proliferation of the cells of the glomular tuft and Bowman's capsule, with more or less lobulation of the glomerulus. It was not possible to resolve any of these cases into the distinct types of intracapillary and capsular glomerulitis; the two conditions were generally combined. In all of these cases there was more or less granular material, evidently coagulated serum, in the capsular space. In the tenth case there was extensive necrosis of the glomeruli with hemorrhage into the capsule, and in the eleventh the capsule was filled with hyaline material, in which both fibrin and red blood-corpuscles were contained. The average duration of these cases was greater than that of those with the interstitial form.

*Lymph Nodes.* Bronchial, cervical, mesenteric, axillary, and inguinal lymph nodes were examined. The most marked lesions were found in the cervical and bronchial lymph nodes. Two types of lesions were observed: first, those which may follow an injury of almost any sort, consisting of congestion, hemorrhage,

diffuse and circumscribed necrosis; second, lesions which belong distinctly to diphtheria, but which may also be found, in a less marked degree, in any other acute infectious disease of children. These lesions consist of a proliferation of the endothelial cells of the lymph nodules and of the endothelial cells lining the sinuses. These cells are phagocytic, engulfing and destroying principally the lymphoid cells, thus giving rise to the nuclear detritus, which is so characteristic a part of the lesion. These lesions are due to the toxic products of the diphtheria bacilli, the bacilli themselves seldom being found in these structures.

*Tonsil.* Changes in the lymphoid tissue of the tonsil are similar to those of the lymph nodes generally.

*Thymus.* The principal change found here was degeneration of the lymphoid cells, especially about Hassall's bodies. The degenerated cells were frequently contained in large cells of the endothelial variety. Eosinophile cells were very numerous.

*Bone-marrow.* Marked hyperplasia, with great increase of cells resembling plasma cells, was the constant lesion. Lymphoid cells were comparatively few in number, and polymorphonuclear leukocytes still less numerous. Eosinophile cells were very abundant in early cases, less frequent in late cases. Apparent transition forms between the cells resembling plasma cells and the eosinophile cells were seen. A few endothelial cells with phagocytic properties were found. The so-called plasma cells were frequently found in the veins. "It is possible that the ordinary marrow cell is the same as the plasma cell."

*Central Nervous System and Skeletal Muscles.* Examination in a small number of cases showed local and diffuse fatty degeneration.

The pancreas, adrenals, testicles, thyroid gland, salivary glands, and pituitary body showed no changes of importance.

March 14, 1901.

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### Experimental Dysentery in Dogs, with Exhibitions of Microscopic Specimens.

H. F. HARRIS, M.D.

During a recent investigation I made numerous attempts to induce experimental inflammations in the intestines of dogs by the rectal injection of various bacteria, and fecal matter from indi-

viduals suffering from dysentery. Among the organisms experimented with are the so-called typhoid bacilli, colon bacilli, the ray fungi, anthrax bacilli, the staphylococci and streptococci of supuration, the mixed bacteria that were grown from the feces of individuals suffering from dysentery, and the so-called bacillus dysenteriae of Shiga. As a general rule, several dogs have been experimented upon with each of the organisms mentioned. In a number of cases they were quite young, and therefore presumably somewhat more susceptible than older animals. In order to prevent the injected material from being at once expelled, in almost every instance the dogs received morphin hypodermatically an hour or so before the bacteria were introduced into their intestines, and there can be no doubt that in practically all cases the microorganisms were retained in sufficient quantity to furnish a reasonable test of their pathogenic power. Bouillon cultures of the bacteria were in most instances used for the experiments, though in some cases the organisms were removed from the solid media and thoroughly ground up with sterilized water in a mortar before being injected. As a general rule 10 c.c. of the bouillon cultures were administered, but in some cases the amount was greater and in some less. A record of the time, the quantity of bacteria injected, and the size of the dogs experimented upon was carefully kept in every instance, and the subsequent histories of the animals were likewise preserved. A study of these records shows that not in a single instance did a dog develop an inflammatory condition of the intestine following the injection of bacteria, and in most cases they were entirely healthy for weeks, and even months, thereafter. These results are of much interest, particularly as regards the organism supposed to be the cause of the acute dysentery of the East—the bacillus first described by Shiga. The cultures used were obtained from Prof. Simon Flexner, of the University of Pennsylvania, to whom I desire to express my thanks. It seems significant that these organisms entirely failed to produce any effect on four 10-day-old puppies, into the large intestines of which they were injected, nor did any disturbance follow when they were introduced into the large intestines of three cats.

Much more satisfactory were the results obtained by injecting fresh feces of individuals suffering from dysentery into the large

intestines of puppies, for in every case in which this was done a typical dysentery immediately developed that resulted in the death of the animals, except in one instance, where the dog was killed. In two cases there were several liver abscesses. It should, however, be stated that no ill effects followed the injection of material of this kind into the large intestines of four large adult dogs and in three cats that were almost grown. It would thus seem that puppies are particularly susceptible to the disease-producing cause of this variety of dysentery. These are not the first successful experiments of this kind, for Hlava<sup>1</sup> induced dysentery in two dogs out of seventeen injected with dysenteric material, and in four cats out of six that had been subjected to a like treatment. Kartulis<sup>2</sup> succeeded in producing dysentery in three cats out of seven, he having injected the stools from patients suffering from dysentery, and also cultures of the ameba.

Numerous attempts were made to cultivate the ameba, but in no instance were they successful. It was therefore impossible to determine what the result would be should these microorganisms be introduced in this state into the intestines of animals, but the experiments of Kartulis, already referred to, indicate that the pathogenic agency exists in cultures containing amebæ made from the discharges of patients suffering from dysentery, and he even asserts that the disease was produced in a cat as a result of the introduction of these organisms in a pure form into its intestine. There seems, however, some tendency among writers to doubt the correctness of his statements concerning the latter experiment, for the reason that no one else has so far succeeded in obtaining these parasites in pure culture.

Since it was impossible to cultivate the ameba, it occurred to me that the next best thing would be to attempt to cultivate all of the bacteria in the discharges of dysenteric patients, and to determine if these mixed cultures were capable of setting up a dysenteric process. Cultures were accordingly made from the feces of the same individuals whose discharges had been used to successfully produce dysentery, and these were then injected into

<sup>1</sup> Hlava. *Centralbl. f. Bak.*, Bd. i., 1887.

<sup>2</sup> Kartulis. *Einiges ueber die Pathogenese der Dysenterieameben.* *Centralbl. f. Bak.*, ix., 1891.

the intestines of four puppies. There was absolutely no effect produced. It therefore seems unreasonable to conclude that the germ that produced the disease is a bacterium, or, at any rate, it seems fairly certain that it cannot be an organism that develops in the culture media ordinarily employed. As the latter supposition does not appear at all probable, and as the ameba coli was the only other living organism found in the feces that was probably absent from the cultures, it seems logical to suppose that this parasite is the cause of any morbid state that the injection of these discharges may give rise to. As will be seen in the microscopic section, this view is supported by the fact that the amebæ are abundantly present in and around the ulcers that are found in the intestines of dogs suffering with experimental dysentery, and it does not appear unreasonable to say that the proof is now fairly clear that these organisms are in reality the causative agents in chronic dysentery.

#### DISCUSSION.

DR. FLEXNER wished to congratulate Dr. Harris upon his successful experiments. He stated that the subject of dysentery was at the present time attracting much attention, and he thought that indications pointed to the existence of more than one form of the disease. The distinction into acute and chronic dysentery was not based upon etiology. Doubtless chronic dysentery was merely a later form of the acute disease which might have more than one origin. On the other hand, there were undoubted examples of chronic dysentery in which the history of the acute onset was wanting. It was that class of cases especially that had been found to be associated with the presence of amebæ in the dejecta. He stated that it might be taken as established that the so-called amebic dysentery differs from other forms of dysentery in its pathologic anatomy as well as in its etiology. On the other hand, the conviction had been growing that the acute dysentery *per se* was not due to amebæ but to certain bacterial species; that the acute dysentery might, moreover, become chronic in nature when the pathologic changes of the intestine were so different from the acute changes that without the history of the disease, and bacteriologic examination, the two might not be considered as belonging together.

It was to this form of dysentery that Dr. Flexner wished especially to refer. He stated that while it was a disease prevalent in the tropics, it occurred also in temperate climates, and not improbably might be found to occur in the United States. His own studies of such cases of dysentery occurring in Manila eventuated in the separation of a bacillus from numerous cases differing from the usual inhabitants of the intestinal tracts, agglutinating with the blood serum of affected individuals, and possessing pathogenic properties for laboratory animals. That organism proved to be identical with a bacillus obtained a short time previous from an epidemic of dysentery in Japan by Shiga. A short time later the organism was obtained from a case of dysentery acquired in Porto Rico, which had lasted for many months, and in which the intestinal lesions, as was afterward shown at autopsy, indicated a chronic process. In a recent publication Kruse, of Bonn, has announced the discovery of an organism probably identical, obtained from an outbreak of dysentery in Germany. Dr. Flexner had recently had an opportunity of studying a case of dysentery in a sailor in Philadelphia in whom he had obtained this organism. The wide distribution of the bacillus, its association with dysentery, its absence from the intestines in a state of health and in some other diseases than dysentery, and the positive specific serum reaction, all rendered highly probable the relation of this bacillus with a particular form of dysentery.

A criticism made by Dr. Harris concerning his experiments made with a culture of the bacillus which Dr. Flexner gave him called for a moment's attention. The bacillus was one which, like so many others, lost its virulence upon long continued saprophytic cultivation. The virulence could, however, be restored by successive passage from animal to animal. In several instances feeding of the bacillus to animals in which the gastric contents had been neutralized caused inflammation of the intestinal tract; but a condition simulating extensive diphtheritic deposits of the intestines in human beings had not been produced experimentally. This was not surprising when it was considered that none of the lower animals were subject to dysentery as it is known in human beings. The imperfection of animals for experiments was, therefore, no just criticism of the importance of this organism in the

etiology of dysentery, and only served to recall similar limitations in the case of the germ of typhoid fever, etc. We were, however, somewhat more fortunate in this case, in that, through an accident, one of Dr. Flexner's laboratory assistants aspirated a small quantity of a culture into his mouth, from which a troublesome and non-fatal form of dysentery was promptly developed; and Surgeon Strong, of the army, had been able to produce the disease in a Filipino prisoner condemned to death who voluntarily submitted himself to the experiment by swallowing a portion of the culture. The organism was recovered from the dejecta.

DR. RIESMAN said that but little could be added to the admirable paper of Dr. Harris and the equally admirable discussion of Dr. Flexner. He had been interested in Dr. Harris' experiments with cats, which evidently seemed less favorable for experiment than puppies. He himself had injected a cat with pus from a dysenteric abscess of the liver, but the cat developed only a transitory diarrhea, and made a complete recovery. The abscess fluid was free from amebæ and was also bacterially sterile. The cat had been injected in the hope that if an ameba was present in an encysted or spore form it might find opportunities for growth in the rectum of the animal, since Quincke and Roos had found the cat very well adapted for the production of experimental dysentery. Dr. Harris was to be congratulated on his success in reproducing in animals the features of human dysentery, even to the production of abscesses. There were very few diseases distinctly human in which this had been done.

DR. HARRIS agreed with Dr. Flexner in holding that there were two forms of dysentery. The amebic form seemed to be a disease of cities, while the other—the so-called "bloody flux" of the South—was common in the country, and rarely became chronic. He thought that the amebic form might begin acutely or subacutely. Whether the amebæ were primarily present or were engrafted secondarily he was unable to say. He did not think that the evidence regarding Shiga's bacillus was positive.

*April 11, 1901.*



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### Cerebellar Lesions without Cerebellar Symptoms.

W. S. WADSWORTH, M.D., W. E. ROBERTSON, M.D.,

AND

W. G. SPILLER, M.D.

*(From the William Pepper Laboratory of Clinical Medicine, Phoebe A. Hearst Foundation.)*

### ABSTRACT.

The case reported by Dr. Wadsworth was one of sclerosis of the left cerebellar hemisphere. Patient had been a strong, capable workman, an ironmoulder by trade. His work required strength, good eyesight, and good coordination of muscles. Two areas of sclerotic tissue, possibly syphilitic in character, were found in the liver.

Dr. Robertson reported a case of tumor of the cerebellum. The patient had been a strong woman, aged thirty-seven years. She began to have severe headache six years before her death. This headache was first felt after a confinement, and was at the base of the brain. She had had this pain from time to time during the six years, although it was more severe after childbirth. She had not had convulsions or disturbance of gait, and there had been no suspicion of disturbance of vision. She had never shown any tendency to fall. She was admitted to the hospital, and had only

been there fifteen minutes when she was suddenly seized with violent convulsions, which terminated fatally in about five minutes.

The second case reported by Dr. Robertson was one of amyotrophic lateral sclerosis. A round tumor about an inch in diameter was found on the corpora quadrigemina, compressing one lobe of the cerebellum, but symptoms of cerebellar disease had not been observed.

The specimens from these three cases were studied microscopically by Dr. Spiller. The most remarkable sclerosis of the cerebellum Dr. Spiller had ever seen was in a case reported by him, in which the cerebellum in its greatest lateral diameter measured one and eleven-sixteenths inch.

Dr. Spiller said that one lobe of the cerebellum is occasionally atrophied as a result of some lesion in the opposite cerebral hemisphere, because each cerebellar lobe is connected with the opposite cerebral hemisphere by both the superior and middle cerebellar peduncles. He had removed a brain in which this secondary atrophy of the cerebellum was very marked. The case was one of right unilateral internal hydrocephalus and the right cerebral hemisphere was a mere sac. The left cerebral hemisphere was normal, but the left cerebellar lobe was much smaller than the right cerebellar lobe, and yet not abnormally hard.

In the specimen removed by Dr. Wadsworth, Dr. Spiller had found the two cerebral hemispheres of equal size, but the left cerebellar lobe was much smaller than the right lobe and distinctly harder to the touch. The various parts of a normal cerebellar hemisphere were present, but not nearly so well developed as in the right cerebellar lobe, and the sclerosis was equally intense in all parts of the left lobe. The zona granulosa and zona molecularis were abnormally narrow, and it was difficult to find any Purkinje's cells in the sections studied from the sclerotic cerebellar lobe. The left corpus dentatum was very small and the nerve-cell bodies within it were atrophied. The entire left cerebellar lobe had a very dense structure, but in no portion was the nervous tissue destroyed. The right inferior olive was much smaller than the left, because the right inferior olive was in connection with the sclerotic left cerebellar lobe by means of the cerebelloolivary fibers.

The tumor of the cerebellum removed by Dr. Robertson was a

cystic glioma. The tumor on the corpora quadrigemina was a fibroma.

Dr. Spiller said that the function of the cerebellum can best be determined by a study of the cases of sclerosis of this organ, as this form of pathologic change produces symptoms more sharply defined than any other. Tumors or abscesses may cause symptoms by pressure on parts not actually injured, and the symptoms so produced may be attributed to the cerebellum. These cases, therefore, are useless for a study of cerebellar function. Suitable cases of cerebellar lesions with necropsy are not numerous, but André Thomas in his thesis on the cerebellum has collected some seventeen cases. If the injury to the cerebellum occurs early in life and is of slow development, or if the condition be one of arrested development, symptoms may be absent; probably because the functions of the cerebellum have been assumed by other portions of the brain. A number of cases have been reported of great defect of the cerebellum with few or no cerebellar symptoms (Otto, F. Fischer, Hitzig, Ingels, Shuttleworth, Doursout, Ferrier). Tumors and cysts of the cerebellum without symptoms of such lesions have been observed. Incoördination is usually present in tumor of the vermis, and it has been supposed that the posterior part of the vermis is more important for the preservation of coördination than the anterior, and yet in the glioma of the cerebellum received from Dr. Robertson the vermis was almost destroyed in its posterior as well as in its anterior portion. The cyst of the vermis was probably secondary to the glioma, but there is some evidence to show that a cyst of the cerebellum may be primary and that a neoplasm may develop in the wall of a congenital cerebellar cyst. The chief interest in the three cases was found in the presence of cerebellar lesions without cerebellar symptoms.

*April 11, 1901.*

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#### A Case of Malignant Endocarditis.

DAVID L. EDSALL, M.D.

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The patient, M. K., was a girl, aged eighteen years, who was admitted to Dr. Stengel's service at the University Hospital on

December 7, 1900. Her family history was of no special interest, and her personal history was interesting only in that she had had an attack of what seemed to have been rheumatism a year before her admission, and had had scarlet fever shortly before that time. There was no history of any sequelæ to these diseases. She had had enlargement of the thyroid for two years and had been taking thyroid extract for five weeks before admission. At the time of admission she complained of gastric disturbance apparently following the use of the thyroid gland, and exhibited the general symptoms of thyroidism. There was moderate irregular fever. She had marked cardiac enlargement with signs of mitral stenosis and regurgitation, the cardiac disease apparently having been present for a considerable period. Until the time of her death, March 3, 1901, she had continuous irregular fever. She exhibited pronounced symptoms of hysteria, which served to add confusion to the diagnosis, and showed no evidences of an acute endocarditis which were sufficient to allow of a definite diagnosis until about one week before her death. The cardiac signs became less pronounced soon after her admission, and the cardiac dulness decreased somewhat in extent for a time, but subsequently reached about the size that was noted upon admission. The cardiac murmurs decreased in intensity, and no new murmurs developed. She had no symptoms of emboli and no skin hemorrhages until six days before death, when there were evidences of embolism of the right iliac, of the left brachial, and of the arteries low down in the left leg, and the next day there were numerous skin hemorrhages. A week before death a pure culture of the streptococcus pyogenes was obtained from blood taken from a vein. She exhibited an advancing anæmia during the course of her illness, the red cells decreasing from a normal count at the time of admission to 2,490,000 shortly before death, and the hemoglobin during the same time decreasing from 80 per cent. to 40 per cent. The condition of the leukocytes was interesting, the first count showing 12,800; the next, made a few days later, showing the same number; during January the count showed only from 6000 to 8000, the leukocytes rising at the end of the month to 14,000 but decreasing again to 9000. A marked and persistent leukocytosis was present only after February 18th, when the count ranged from 24,000 to 38,000, the number tending, after February 18th, to increase constantly. A differential count,

when the leukocytes were recorded as 9900 to the cmm., showed 87 per cent. of polymorphonuclears, 8.7 per cent. of lymphocytes, 1.8 per cent. of mononuclears, 1.8 per cent. of transitional, and no eosinophiles. The chief interest in diagnosis had been between malignant endocarditis and a perirenal abscess. A number of local signs pointed to the latter condition, and in the second week in February numerous small, dark brown spots appeared on the right forearm and hand, and a smaller number on the left arm and hand. There were elsewhere areas of larger pigmentation of lighter color, and it was thought possible that the suspected perirenal abscess had caused disturbance of the suprarenal gland which had resulted in this pigmentation. Melanin was looked for in the urine, using Mörner's method. The result was negative, and several punctures of the renal region were negative. The nature of the case became evident in the last week of life. A post-mortem examination done on March 3 showed numerous infarcts of both lungs, of the spleen and kidneys, and there was a suppurating thrombus in the right iliac artery; the other arteries could not be investigated. The heart was much enlarged, the walls thickened, there was almost complete adhesion of the two layers of the pericardium, the aortic leaflets showed moderate thickening and there were small recent vegetations on all the leaflets, the mitral valves were thickened and contracted, and there was a very large collection of vegetations, chiefly on the auricular surface, which so largely obstructed the auriculoventricular orifice that only a narrow slit less than a quarter of an inch wide and a half-inch in length remained. No collection of pus was found anywhere with the exception of the suppurating thrombus in the right iliac. The thyroid gland was much enlarged, and the cut surface showed numerous small colloid cysts. The tonsils could not be examined postmortem, but during life they appeared to be practically normal. Cultures taken at the postmortem from the heart's blood, the vegetations on the valves, the lungs, the spleen and the kidneys all showed the presence of the streptococcus. Cultures from the lungs and the heart's blood and valves also showed a bacillus and a large coccus. Sections from the vegetations showed large collections of bacteria of the three forms mentioned.

All the cultures were made by Dr. S. S. Kneass.

*March 28, 1901.*

## The Estimation of the Urinary Sulphates and of the Fecal Fat in the Diagnosis of Pancreatic Disease.

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### ABSTRACT.

The possibility that a reduction of the ethereal sulphates of the urine might be a valuable sign of pancreatic disease has previously been referred to in these proceedings (New Series, vol. ii.) by A. E. Taylor. The reason that the test was first used is that bacteria flourish on the products of digestion of albumin, while they have apparently little action upon native albumin, and bacteria are through their further action on the products of digestion of albumins the chief producers of the substances which ultimately are excreted as ethereal sulphates; if then the proper food of the bacteria is reduced in quantity through absence of pancreatic digestion, the ethereal sulphates may reasonably be expected to be reduced. Several observers claimed that a reduction of the indican in the urine or its absence is indicative of pancreatic disease, but varying and unsatisfactory results have been obtained with this rough test. Le Nobel, who first investigated the condition of the total ethereal sulphates in man, found them almost absent in a case in which it was nearly certain that pancreatic disease was present. A. E. Taylor recorded their marked reduction in a case in which there was probably pancreatic disease. Neither Le Nobel nor Taylor could report a postmortem confirmation of the diagnosis. Northrup and Herter noted the absence of the reduction of the ethereal sulphates in a case in which operation showed what seemed to be a growth of the pancreas; it was not definitely known whether the pancreatic duct was obstructed. No other observations of human subjects seem to have been reported. The experimental work of Katz and others has shown varying conditions of the ethereal sulphates after operations upon the pancreas, even when this organ was completely removed. I carried out the test in two cases, one being proved by postmortem examination to be carcinoma of the pancreas with complete obstruction of the duct, the other being shown by the clinical course to be a case of pro-

longed catarrhal jaundice without any evidence of involvement of the pancreas. In the case of pancreatic carcinoma the estimation of the sulphates on two days gave the following figures: Preformed 2.495 grams, ethereal 0.085 grams; on a second day, preformed 3.208 grams, ethereal 0.115 grams. The ratio between the ethereal and the preformed sulphates on the two days was 1 to 29.4 and 1 to 20; the ethereal sulphates were therefore much reduced, and their ratio to the preformed sulphates was much less than normal. In the other case, in which pancreatic disease was absent, the figures on two days were: preformed 3.268 grams, ethereal 0.440 grams; on the second day, preformed 3.792 grams, ethereal 0.444 grams; the ratio between the two on the first day being 1 to 7.4, on the second day 1 to 8.5. The ethereal sulphates were therefore absolutely and relatively increased. These results and those of Taylor and Le Nobel seem to indicate that the sign may be a valuable one, and investigation of human subjects is certainly more valuable than animal experiments in which the conditions produced do not nearly correspond to those seen in human disease. It is highly probable, however, that the intestinal bacteria are able to break up undigested albumins sufficiently to keep the amounts of ethereal sulphates excreted in the urine equal to or perhaps greater than the normal, even in the absence of pancreatic secretion from the intestine; hence, a negative result of the test is probably valueless for this reason. It must also be remembered that a growth of the pancreas may furnish secretion to the intestine even when the pancreas proper is largely destroyed, providing that the duct remains open; and a small amount of pancreatic secretion may be sufficient to render the test negative. Therefore, only a positive result of the test can be expected to be of value. Also the presence of certain factors in the individual case would render even positive results of uncertain value; gastric hyperchlorhydria, diarrhea, and milk-diet have been shown to be frequently associated with very low values for the ethereal sulphates, and the presence of these factors would greatly limit the value of the test. But in their absence, and particularly in the presence of constipation, gastric hypoacidity, or anacidity, icterus, grave anemia or cachexia a positive result of the test would seem to be of decided value in the diagnosis of pancreatic disease. All the factors

last mentioned tend to increase the amount of ethereal sulphates in the urine, and all these were present in the first case reported, and yet the amounts of ethereal sulphates were very low. In that case, therefore, the test was considered to be of importance in diagnosis, and it seems probable that it may be of aid under similar circumstances.

The general clinical teaching concerning the relation of fatty stools to the diagnosis of pancreatic disease seems to be based on the incomplete and partly incorrect statements of earlier investigators. Almost all treatises on pancreatic disease as well as the textbooks on the practice of medicine and on clinical diagnosis insist that the presence of an excessive amount of fat in the stools is important evidence of the existence of pancreatic disease. It has nevertheless been shown very positively, chiefly through the work of Müller, that icterus is practically always accompanied by the excretion of fatty stools, and the same author and others have demonstrated that severe disease of the intestine so disturbs fat absorption as to give the same result. If then there is in any case under consideration severe disease of the intestines, or if icterus exists, the presence of fatty stools is of no importance in deciding whether pancreatic disease is present or not, and in a very large percentage of cases of pancreatic disease there is either icterus or marked intestinal disturbance. Hence, this sign is one of very limited importance unless observed in the absence of icterus or intestinal disturbance or in connection with other signs which point strongly toward the pancreas, such signs being persistent glycosuria, tumor in the region of the pancreas, and marked coincident disturbance of the absorption of proteins. In the second case which I mentioned, that of protracted catarrhal jaundice, the fat absorption was investigated. The fat in the diet, which consisted solely of milk, was determined daily; the stools were collected, and after evaporating the water, were completely extracted by ether in the Soxhlet apparatus. The stools when warmed were oily in appearance, and were fluid even after the water had been driven off; ether extraction showed that the feces of three days contained 154.18 grams of fat, while the total weight of the feces in this time was 184.69 grams. Therefore, 83.84 per



cent. of the dry feces was fat. During the same period the patient took 250.8 grams of fat, and since the total amount in the feces was 154.18 grams she lost 61.6 per cent. of the fat ingested, while normally as much as 90 per cent. is absorbed. This patient had marked jaundice, and the further course demonstrated that there was no pancreatic disease. The case is, therefore, further testimony of the correctness of Müller's statement that icterus causes severe disturbance of fat absorption, and that if icterus is present the loss of a large amount of fat in the feces is not a direct indication of pancreatic disease. Müller considers, however, that the presence of a very large percentage of neutral fat in the feces is an indication of disease of the pancreas, as it indicates that the splitting of fats which is normally performed chiefly by the secretion of this organ has not been carried out; according to his experience a disturbance of the fat splitting action occurs only in cases of pancreatic disease and is therefore an indication of such disease. In the case just mentioned, in spite of the large fat loss in the feces, there was no disturbance of the splitting of the fats: 78 per cent. of the fats present in the feces was found to be fatty acids and soaps, while only 22 per cent. was neutral fat. This is confirmatory of Müller's statement that icterus does not interfere with the splitting of the fats. The case of pancreatic carcinoma could not be studied in this connection, as the stools were not preserved owing to error of a nurse. So far as investigations have been carried they indicate that Müller's view is usually correct, but investigations have been very few in number, and at best this method is a difficult one to use for purposes of clinical diagnosis, and is not likely to be of general value to clinicians.

*April 11, 1901.*

### Primary Tuberculosis of the Pericardium.

DAVID RIESMAN, M.D.

#### ABSTRACT.

Tuberculosis of the pericardium usually presents itself either in the form of scattered miliary tubercles or as a tuberculous infiltration, with great thickening of the pericardial layers; rarely as a serous, serofibrinous, purulent, or hemorrhagic pericarditis. In miliary

tuberculosis the nodules are found most abundantly near the base of the heart or on the parts reflected upon the great vessels. The process, as a rule, is merely an incident in a general tuberculosis and possesses no clinical importance. The tuberculous infiltration is either associated with abundant serofibrinous exudation or with a more or less extensive cohesion of the pericardial surfaces, and not infrequently with great thickening of the layers and complete obliteration of the sac. The heart then looks as if encased in a cuirass. On cursory, naked-eye examination, the appearances are often not in the least characteristic of tuberculosis. Sometimes, if the process is recent, a careful separation of the layers may reveal, here and there, miliary tubercles or larger cheesy conglomerates; but in old cases of pericardial symphysis the familiar picture of tuberculosis may be so completely obliterated that the most careful inspection with the unaided eye fails to reveal the true nature of the process. It is only the microscope that under these circumstances can definitely demonstrate the tuberculous character of the pericardial disease. In rare instances, as in the one reported by Kast, tuberculosis produces a purulent pericarditis. A very unusual case is also recorded by Eichhorst; the pericardium was the seat of three ulcers that had all the appearances of tuberculous ulcers such as are seen in the intestine. In many instances the fluid is hemorrhagic. This was so in the remarkable case of Musser, in which the pericardium contained 64 ounces (2 liters) of blood; in the analogous case of Hirtz the sac contained 2790 c.c. of bloody fluid.

From the point of view of etiology we may divide tuberculosis of the pericardium into the following forms:

1. That which is a part of a general miliary tuberculosis.
2. That associated with general serous-membrane tuberculosis (tuberculous polyserositis).
3. That due to extension from neighboring organs, as the lung, the pleura, the mediastinal and peribronchial lymph glands, the bones (vertebræ, sternum, ribs), and the myocardium.
4. That developing independently.

The first needs no special consideration, as the pericardial tuberculosis is entirely subordinate to the terminal systemic infection. Pericarditis as a part of general serous-membrane tuberculosis is

not common ; more often the pleura and peritoneum are involved together, the pericardium escaping ; but in rare instances all three serous membranes are implicated. The tuberculosis in these cases presents itself either as an acute miliary tuberculosis or as a chronic fibrous process.

The majority of cases of well-marked pericardial tuberculosis are the result of extension from neighboring tuberculous foci ; most frequently from the mediastinal and peribronchial lymph glands. Weigert, to whom we owe the demonstration of this fact, showed that, as a rule, the pericardial disease has its origin from lymph glands situate on the interior layer of the pericardium in the anterior mediastinum or from those found at the point of reflection of the pericardium. In the case of Kast, previously mentioned, a gland belonging to the group placed about the aorta and the pulmonary veins, near the posterior surface of the pericardium (the subbronchial glands of Baréty) had perforated into the pericardial sac.

Ordinary pulmonary tuberculosis does not often lead to pericarditis. Leudet found it only 8 times in 299 autopsies. In the experience of Willigk it was still rarer—11 times in 1317 autopsies on phthisical cases. Louis found it 3 times in 112 cases.

In the presence of well-marked tuberculosis of any of the neighboring organs we should always suspect an associated pericarditis, particularly if obliterative, to be tuberculous in origin ; but in the absence of well-marked tuberculous disease elsewhere there is often nothing to call attention to the possibility that a pericarditis in a given case may be tuberculous. Hence, it is probable that cases of tuberculous pericarditis are often recorded as simple forms of pericardial inflammation. Some of these may belong to the fourth group—that of primary tuberculous pericarditis.

In the case which I beg to report, the appearances at autopsy were not at all suggestive of tuberculosis ; yet the microscope revealed lesions typical of that disease. The patient was thirty-two years of age, white, of healthy parentage, an iceman by occupation. He entered the hospital with signs of an acute pericarditis, there being a well-marked, to-and-fro friction sound. This latter eventually disappeared, but the patient grew worse, had severe dyspnea on slight exertion, was more or less cyanosed,

and seemed excessively peevish. The heart sounds were feeble at the apex and quite loud at the base; the apex was not visible nor palpable; the pulse was rapid and feeble; the temperature varied from normal to  $101^{\circ}$ . The left pleural cavity was tapped and a quart of bloody fluid withdrawn. A little of this fluid was injected into a guinea-pig. The signs of heart failure gradually grew more marked, but there was no endocardial murmur at any time and no signs of pericardial effusion. A diagnosis of adherent pericardium was therefore made. The insidious onset and the bloody character of the fluid in the pleural cavity suggested that the pericarditis was tuberculous in origin.

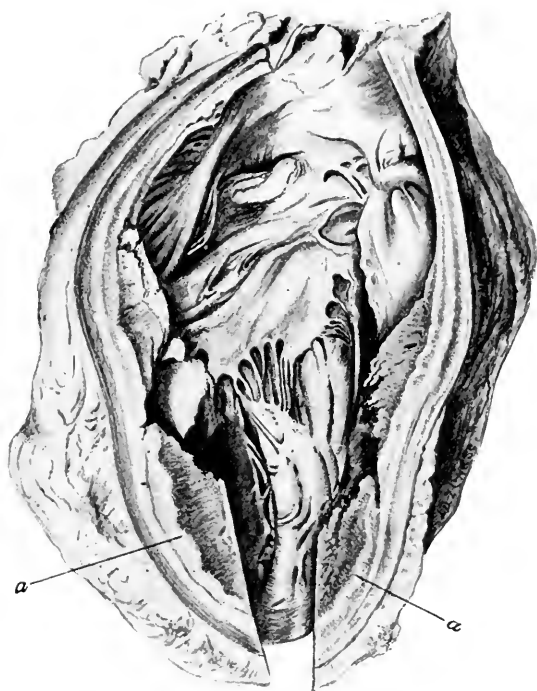
The patient died suddenly, and at the autopsy complete obliteration of the pericardial sac was found. The pericardial layers were enormously thickened and firmly glued together by new tissue. There was no sign of tuberculosis in the heart at autopsy. A small healed tubercle was found in the right lung. The right pleural cavity was obliterated by adhesions. The left contained a large amount (1800 c.c.) of serous fluid, having a specific gravity of 1017. There were a few peritoneal adhesions. The heart was hypertrophied, and, with the pericardium, weighed 580 grams. The liver was adherent to the diaphragm, and showed, as did also the kidneys, considerable congestion.

The guinea-pig died before the microscopic examination of the patient's heart had been made, and was found to be tuberculous. Death occurred four months after the inoculation and one month after the demise of the patient.

Microscopic examination of the man's heart showed extensive tuberculization. There were caseous areas, giant cells in large numbers, epithelioid cells, and round cells. Tubercle bacilli were not found, probably on account of imperfect preservation of the specimen. Staining for elastica showed that the intercalated new tissue was free from elastic fibers. Newly-formed bloodvessels were abundant in the deeper layers of the visceral and parietal pericardium, but did not penetrate the tuberculous tissue between the two.

To all appearance the tuberculosis in the pericardium was primary, there being no tuberculosis in the lung except the small tubercle, nor in the pleura, nor anywhere else. It is possible,

perhaps probable, that the tubercle bacilli came from the focus in the lung. If that is true, then the pericarditis is anatomically not a primary disease; clinically, it was primary. But it is also possible that the tubercle bacilli entered elsewhere and left no trace behind them, in which case the pericarditis would be primary also in the anatomic sense.



Primary tuberculosis of the pericardium; obliteration of pericardial sac; great thickening of pericardial layers. *a a*. Right ventricle cut open.

In an analysis of 778 autopsies held in the Philadelphia Hospital during the past three years and nine months, there were 60 cases of pericarditis (7.7 per cent.). Of these, 20 were examples of adherent pericardium. In none of the 20 had any note been made as to tuberculosis; but as a large number occurred in cases in which there was well-marked pulmonary tuberculosis, we may infer that in some of them the pericarditis was also tuberculous. This shows what I have before emphasized: that a microscopic

examination is sometimes necessary to determine the nature of a pericarditis.

The question of the effect of pericardial symphysis upon the size of the heart has often been discussed. Of 17 of the Philadelphia Hospital cases in which the weight of the heart was given, there was hypertrophy in 7. Of these 7, there were 2 in which the hypertrophy could clearly be attributed to the adherent pericardium. We may infer then that pericardial adhesions can produce hypertrophy, but that other contributing factors are often present.

#### DISCUSSION.

DR. SAILER inquired whether, in the cases collected by Dr. Riesman, the pericardium had been weighed with the heart, and whether the *pulsus paradoxus*, which is considered a sign of adherent pericardium, had been present.

DR. WOLDERT stated that he had this year seen a specimen of tuberculous gland of the mediastinum removed by Dr. Kirkbride at autopsy from a case at the Philadelphia Polyclinic. This tuberculous focus had ruptured into the pulmonary artery and terminated in miliary tuberculosis and death within a few days.

DR. STEELE considered it very interesting that tubercle bacilli were obtained from the pleura, although at autopsy no tuberculosis of the membrane was found. Two explanations seemed to him possible: (1) That there was some focus of tuberculosis in the pleura; (2) that the effusion had been passive and that, while it was at its height, there was a general circulation of tubercle bacilli. He thought that all parts of the pleura should be carefully examined.

DR. ANDERS believed that adherent pericardium was usually followed by hypertrophy, although a recent observer, whose name he could not recall, had stated, after an examination of a large number of hearts, that this was not the case. The precise relationship between adherent pericardium and cardiac hypertrophy had not as yet been satisfactorily established. Fatty infiltration of the heart might also be a consequence of adherent pericardium.

DR. WADSWORTH had seen three cases of adherent pericardium, in all of which the heart was hypertrophied. Regarding the ques-

tion of hypertrophy, it was, however, to be remembered that the term was a relative one, and that the size of the body had to be taken into consideration; what was hypertrophy for one would not be for another. Anything interfering with the heart's action, he thought, would tend to cause hypertrophy.

DR. COPLIN said that he had the opportunity of examining the specimen in a fresh condition, and that he did not suspect the presence of tuberculosis. He had long ago lost any fear of serous membrane tuberculosis, and was convinced that it often completely recovered. A recent observer had compared tuberculosis of serous membranes with that of the skin, maintaining that the endothelium behaved like the epithelium in that lesion.

DR. RIESMAN, in closing the discussion, said that statistics were, as a rule, more or less unreliable; the pericardium had always been weighed with the heart. In deciding upon the presence or absence of hypertrophy he had taken an arbitrary standard, and had considered hearts weighing, with the attached pericardium, above 450 grams, as hypertrophied. In the cases he had collected he had also been guided by the statement of the pathologists that the heart was hypertrophied. The pulsus paradoxus had not been present.

*December 27, 1900.*

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I. Pachymeningitis Interna Hæmorrhagica. II. Tumor of the Spinal Cord.

F. SAVARY PEARCE, M.D.

ABSTRACT.

Two specimens were presented: One from the case of a man, aged seventy-one years, who died in the medical wards under the care of Dr. James Tyson, and the second specimen from the case of a man, aged thirty-eight years, who died in the service of the writer in the nervous wards of the Philadelphia Hospital. Both of these specimens were unilateral, which, according to Osler, occurs in 50 per cent. of the cases. The first case was admitted on February 21st and died on March 15, 1901. The patient was brought in, suffering from right hemiparesis, which, after some days

cleared up to such an extent that the patient was able to walk about, finally dying of a complicating nephritis. At the autopsy the dura mater was found quite adherent to the skull over the left hemisphere, and internal hemorrhagic pachymeningitis of large extent was determined. The blood was clotted and somewhat laminated, showing the evidence of chronic pathologic processes. The hemisphere below was somewhat compressed and the lateral ventricle was collapsed. The brain itself was normal, the hemorrhagic area extends, as you see, over the whole superior and external portion of the left hemisphere, descending to the level of the fissure of Sylvius.

My own case gives a history of chronic alcoholism, and with the further history that would make for suspicion of disease of the dura for the past three years. During this time he had complained of feebleness in the upper extremities, so that he could not hold tools in his stiffened clasp. At this time, too, he began to complain of pains running up and down both lower extremities. Shortly after this he says his extremities became stiff, and this has persisted from that time. About two months previous to admission, on March 4, 1901, he developed incontinence of urine, which has persisted. Upon examination, the right pupil was smaller than the left, both reacting sluggishly to light; the tongue was protruded straight; speech slow; patient in condition of mental stupor, with a slow, intermittent pulse; knee-jerks were exaggerated, but spasticity so great that ankle clonus could not be obtained. There was no Babinski sign, and the spasticity was greater in the left leg and foot and arm than on the right. Sensation to pain and touch was absent over the left foot and leg up to a point above the knee. The arms were the most spastic of the extremities when compared with the legs. The patient can be lifted from the bed during forcible extension of the forearm, permitted through contraction of the scapula and trapezius muscles. Spasticity is of lead-pipe quality, and persistent.

On March 8, 1901, the mental condition was sufficient to get the following data: The patient, speaking in low staccato voice and complaining of a feeling of drowsiness, complained of intense pain in the temples, and upon examination it was determined that the pupils responded to accommodation, but not to light. The



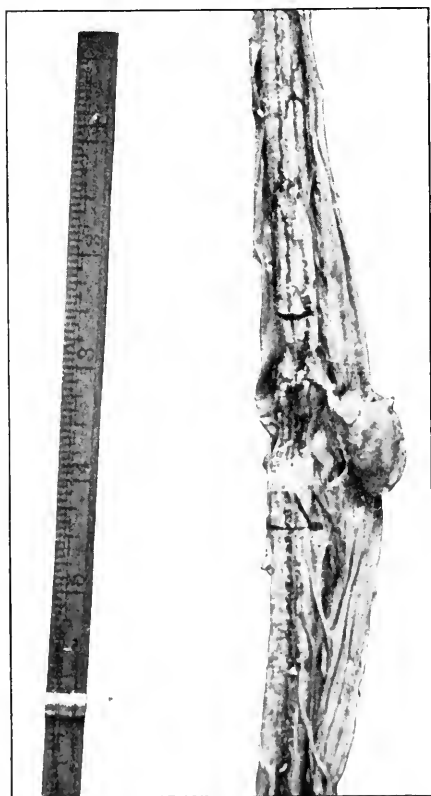
left arm was completely paretic, the left leg being spastic, though palsied to a much less degree. The breathing was labored. The patient's condition alternated from wandering delirium to coma, but the palsy remained practically the same; the breathing became shallow, the temperature rising to 103° F., and he died on March 16th of exhaustion.

*Autopsy.* Upon opening skullcap considerable blood escaped and a large hemorrhage was found. This proved to be subdural and on the right side. It extended from the occipital to the frontal lobe and downward to the Sylvian fissure, extending into the latter so as to separate the temporal and opercular convolutions from the island of Reil. A glass held below the skull as the brain was removed collected 50 c.c. of blood and cerebrospinal fluid. When the dura mater, containing also a large laminated clot, was removed, the surface of the brain was considerably flattened, therefore must have been under considerable pressure. The vessels of the pia were deeply congested. On opening the left lateral ventricle, it was found distended with cerebrospinal fluid. The lateral ventricle of the right side was compressed so as to be almost occluded. The choroid plexus of left side terminated in a soft tumor the size of a soup-bean.

#### TUMOR OF CORD.

The tumor of the spinal cord was taken from a white woman, aged sixty-one years, who died of erysipelas on February 7, 1901. She was admitted to the nervous wards of the Philadelphia Hospital on November 22, 1898, when she complained of stiffness of the lower extremities and inability to walk. The case was diagnosed as one of myelitis. Some points in the progress of the case to be especially noted were: Extreme spasticity of the lower limbs with marked adduction and rotation of the legs. There was no ataxia of the arms; the tests for sensation were always unsatisfactory on account of the patient's mental incapacity, but there appeared to be delayed sensation in the legs below the knees, and she complained pretty constantly of pain shooting down the legs, which, with contractions, frequently kept her awake nights. The Babinski sign was present in both feet. The pupils were equal and responded

to light and accommodation. There were no extra-ocular palsies. The sphincters were involved at times, not constantly. The patient developed bed-sores in January, 1901, at which time the incontinence of the vesical sphincter was persistent. There was no albumin or sugar in the urine.



Tumor (psammoma) pressing into the spinal cord (ventral aspect).

At autopsy a beautiful specimen, as you see, of subdural pedunculated tumor, and pressing firmly into the ventral aspect of the lower dorsal cord, was found. It measured one inch by a little over half an inch, was granular macroscopically, and nonvascular. The spinal cord showed evidence of chronic myelitis and degeneration from the pressure so long existent. Section of the tumor

by Prof. Jos. McFarland shows it to consist of groups of endothelial cells with numerous pearly bodies disseminated throughout. The origin of this psammoma was, in all probability, from the central canal of the spinal cord, which, according to the theory of Cohnheim, would have the germinal cells thus excluded from the central canal by the embryologic defect that he styles exclusion. It is doubtful whether this tumor could be removed, lying, as it does, on the anterior aspect of the cord.

*May 9, 1901.*

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### The Increase of Elastic Tissue in the Lung in Chronic Passive Congestion.

RICHARD MILLS PEARCE, M.D.

#### ABSTRACT.

Elastica is found normally in all parts of the lung; beneath the pleura, in the intrapulmonary septa, bronchi, bloodvessels, and throughout the walls of the air cells.

In chronic passive congestion an increase of elastica is found in all these locations. The most characteristic appearance is seen at the vestibule and air sac passage, where the augmented elastica forms dense nodular projections. The increase throughout the walls of the air cells is very great.

This increase of elastica undoubtedly explains the peculiar firmness of the lung in chronic passive congestion. The purpose, apparently, is to support the overfilled capillaries and prevent collapse of the walls of the air cells.

*April 25, 1901.*

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### Teratoma of the Testicle.

WM. F. HENDRICKSON, M.D.

#### PRELIMINARY NOTE.

The following report gives the pathologic findings in a testicular tumor removed from a young man, twenty-five years of age, by Dr. Martin. The right testicle, apparently, was the only structure

involved by the new growth. Unfortunately, no clinical history is at this time available.

The tumor consists of an extirpated testicle and the adjacent portion of cord. It is approximately pyriform in shape, measuring  $8 \times 5.5 \times 5$  cm. in extent. The visceral tunica vaginalis is almost normal in thickness, but at the upper extremity there are adhesions between this tunic and the parietal layer.

The adhesions completely surround the crater, which lies around the cord, and extend to the surrounding tunic for a distance of 3 cm. in each direction. The two tunics can be separated from a fibrous tissue, partly necrotic, which seems to unite them. Projecting from the surface of the testicle, covered by the tunica vaginalis on one side, are two excrescences of dome shape, the larger measuring  $22 \times 20$  mm. in superficial area. They are bluish in appearance and of soft texture. Adjacent to the larger of these is an elevated yellow nodule, the size of a canary seed and in the tunica albuginea. This had been hidden by the adhesions to the parietal tunica vaginalis. It is evidently a small mass of tumor growing through the tunic, and suggests that the tissue uniting the two may also be tumor.

On laying open the testicle the main tumor mass is revealed. Nothing of the original testicular tissue remains as far as can be made out. The whole mass consists of firm, semitranslucent and degenerated material. It is not easily torn except where degenerated. There is considerable variation due to degeneration. Coarse bands of grayish-white fibrous tissue run through the tumor, and between these, tissue, semitranslucent and gray or opaque yellowish-white or reddish (where hemorrhage has occurred), is found.

The dome-shaped masses described, on section, consist of a spongy network of vessels embedded in pinkish tissue. The vessels themselves have well-formed walls.

Microscopically the tumor reveals a varied structure, consisting of perivascular growth for the most part, but also, in places, of dense connective tissue, cartilage, and epithelial structures.

The most striking portion, the perivascular growth, shows a most complicated arrangement—such that an examination of the growth about large vessels is useless, and, therefore, a clue must

be sought where the vessels are smaller. About the smaller vessels is found a new growth of cells, epithelioid in character, and from one to three or four cells thick, and for the most part quite regular and uniform in distribution.

About slightly larger vessels the border of the perivascular growth reveals considerable irregularity, and in many places distinct papillomatous processes occur. The central portion of these papillæ is formed by a connective tissue prolongation with a blood-vessel from the primary vessel wall. Study of larger vessels reveals this arrangement always present, becoming more and more complex.

The growth at once suggests a formation of bloodvessels, which, as they spring into existence, become surrounded by epithelioid cells.

The vessels next larger in size show the final stage of growth. These reveal the smaller dependent vessels anastomosing again and again. Each small vessel with its connective coat about anastomoses with an adjacent twig, and each being surrounded by a zone of epithelioid cells, the resulting picture approaches somewhat a glandular structure in appearance. This network of vessels with surrounding cells exists as a zone about the larger primary vessel.

Because of the character of growth, viz., anastomosing vessels with surrounding epithelioid cells, small spaces naturally exist between adjacent vessels. Many of these spaces are completely empty, but others show considerable precipitated serum, suggesting lymph spaces.

Beyond the zone of cellular growth just described, and separating neighboring zones of other vessels, is found connective tissue which is directly continuous with that of the vessels. In places it is dense and almost nonvascular, but elsewhere edematous.

The above description applies to the main portion of the tumor. Elsewhere, however, structures of an entirely different character are found.

Embedded in a dense connective tissue and irregularly placed are several pieces of hyaline cartilage. At another point is found a large cyst-like cavity lined with stratified epithelial cell, which have in portions undergone extensive keratinization with marked desquamation.

Along the free border of some sections a structure suggestive of adrenal was discovered. This formation reveals an elongated mass of cells very much like those found in the cortex of the adrenal. Throughout the mass numerous giant cells of the foreign body type are found. From one side numerous small blood-vessels and connective tissue cells enter and penetrate throughout.

In conclusion we may briefly state the chief points of interest in the tumor are the presence of an anastomosing angiosarcoma, with a perithelial proliferation, giving rise to gland-like and papillomatous proliferations associated with connective tissue and cartilage growth as well as epithelial-lined cysts and adrenal-like structures.

*May 23, 1901.*

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### Tuberculosis of the Heart.

W. S. WADSWORTH, M.D.,

AND

W. F. HENDRICKSON, M.D.

The specimen is a heart obtained in the service of Dr. Wadsworth. The subject was a negro, about thirty-four years old, who had had no recent illness of importance. He had, however, been complaining in an indefinite way for some months.

At autopsy, interest in the case was at once drawn toward the heart, the most important notes bearing on the condition being the presence of a few scattered caseous tuberculous nodules throughout both lungs and the presence of a slightly increased quantity of blood-stained fluid in the pericardial sac.

The heart shows the following condition: Weight, 310 grams. It is normal in size and not flabby. The epicardial surface of auricles and right ventricle is everywhere smooth and free from apparent abnormality, except a small milk patch on the right ventricular wall. Over the left ventricle surface a most interesting condition is found. It is everywhere mottled, due to the close crowding of irregularly shaped, grayish-yellow areas, with dark-red intervening heart-muscle. In size these yellow areas vary from a pin-point to several millimeters, and, although lying beneath the epicardium, cause distinct elevations which are too slight to be accurately measured.

On section, the mottled appearance is found to extend throughout the entire thickness of the left ventricle, involving the papillary muscles. The grayish-yellow areas are more irregular in shape in the depth and correspond in places to the circular distribution of the myocardial fibers. The whole condition is diffuse.

At one point in the posterior wall of the left ventricle, near the ventricular septum and 1 cm. below the level of the auriculoventricular groove, there is found a grayish-yellow nodule, roughly 1.5 cm. in diameter. The border of the mass is not absolutely sharply defined. There is a distinct tendency for the nodule to project above the surrounding myocardial tissue, and, on palpation, the consistency is found distinctly firmer.

Everywhere over the endocardium of the left ventricle can be seen grayish-yellow areas, small in size, and corresponding in general to the appearance described for the epicardium.

The left surface of the ventricular septum reveals a mottled area, measuring 1 cm. wide, 3 cm. long, and lying directly below the right attachment of the anterior aortic cusp, and about 1 cm. below the base of this cusp. The long axis of this area lies parallel to the long axis of the heart. Section of this region discloses immediately beneath the endothelial surface a grayish-yellow mottled appearance similar in all respects to that described above for the left ventricle wall.

Beneath the endocardium of the left auricle is found a large, bright-red hemorrhage, 1 cm. in diameter, and lying just above the anterior cusp of the mitral valve.

Examination of heart-valves is negative. Over the aortic wall are scattered a few patches of sclerosis. The coronary arteries likewise show only a few areas of thickening.

<i>Measurements.</i>									
Thickness of left ventricle wall	.	.	.	.	.	.	.	.	11 mm.
Thickness of right ventricle wall	.	.	.	.	.	.	.	.	3 mm.
Valves, mitral	.	.	.	.	.	.	.	.	10 cm.
" tricuspid	.	.	.	.	.	.	.	.	11 cm.
" aortic	.	.	.	.	.	.	.	.	8.5 cm.
" pulmonary	.	.	.	.	.	.	.	.	9 cm.

Microscopic sections taken from various portions of the left ventricle wall show the condition to be that of tuberculosis. Quite a few miliary tubercles are found, the cells composing these being

epithelioid, numerous round cells, and an occasional giant cell of tuberculous type. A few polymorphonuclears and eosinophiles are also present.

For the most part, however, sections show extensive diffuse infiltration of the entire myocardium, with large numbers of epithelioid, small round cells, and giant cells. There are also numerous plasma cells, polymorphonuclears, and eosinophiles, the picture, as a whole, representing a very striking condition of diffuse tuberculous myocarditis.

The distribution of the areas of infiltration is only fairly regular. In some places the growth is confined entirely to the coarse connective tissue bundles running between the heart-muscle; the greater portion, however, shows marked infiltration between individual muscle cells.

The muscle fibers, as a result of this growth, have undergone marked atrophy. The pigment, on the other hand, occupies a relatively large area of the muscle cell. The cross striations in most places are well retained. Many bloodvessels showing great congestion are found everywhere throughout the sections. They are found in the diffuse tuberculous tissue as well as in the comparatively unaffected portions, and evidently represent the pre-existent vessels of the part.

Throughout the tuberculous tissue retrogressive changes are found in many places and are represented by small areas of caseation corresponding to the centers of miliary tubercles as well as by large irregular areas involving the more diffusely distributed new growth.

A guinea-pig inoculated subcutaneously with a small portion of the fresh heart tissue was found dead about four weeks after inoculation. Autopsy revealed no enlargement of the lymph nodes or other manifestation of tuberculosis. Repeated staining of sections to demonstrate tubercle bacilli was also made with entirely negative results.

In view of the microscopic appearances, however, even though the inoculation test and demonstration of the tubercle bacillus were negative, the specimen must be regarded as a diffuse tuberculous myocarditis.

*May 23, 1901.*



# Proceedings

of the

## Pathological Society of Philadelphia.

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### Symposium on Diabetes.

#### General Metabolism in Diabetes Mellitus.

DAVID L. EDSALL, M.D.

The fact that my discussion is to be limited purely to metabolism in diabetes, without considering the relations of the metabolic disturbance to various organs, will necessitate omission of some points which are apparently of extreme importance in connection with the portion of the subject assigned to me. In the case of the pancreas in particular valuable discoveries have been recorded, and knowledge of these is practically essential to a proper conception of present views concerning the nature of the metabolic abnormalities in this disease. Such matters will, however, be more properly discussed by other speakers.

Since so large a number of points must be touched upon in discussing the general metabolism, I must repeatedly throw together facts which are somewhat distantly related in order to accomplish the duty which has been assigned to me within the limit of time.

The whole nutritional difficulty in diabetes, so far as is definitely known, is one that in an ordinary case relates, primarily, solely to the carbohydrates. The sum total of the activity of the metabolic processes is practically normal; and the demand for and expenditure of energy are normal, except in so far as these

are influenced by the disturbance of the carbohydrate "mechanism" Speaking freely, we may say that the diabetic expends the same amount of energy and suffers the same daily amount of tissue loss as a normal person, and requires in his food the same amount of energy and of material for repair as does the normal man. In one small way, to be sure, the diabetic does use, and therefore does demand, more energy than a normal man under the same circumstances. He goes through the labor of digesting carbohydrates, he produces carbohydrates within himself, and he, perhaps, constantly builds up glycogen and then produces glucose from it. All these processes serve a useful purpose in the normal subject and yield far more energy than they consume. In the diabetic, on the contrary, the energy of this labor is wasted, the partially prepared food is cast out without being used and without having furnished in return even the energy which it has itself demanded. Modifying the previous statement, therefore, in slight degree, a diabetic may, in regard to his nutritional demands, be looked upon as differing from the normal person only in that he uses slightly more energy in accomplishing the same amount of work. It is, however, essential to recognize that his real fault does not lie in a pathologically increased expenditure of energy and a consequently increased demand, such as is seen in many febrile and toxic states; it is a fault which does not lie in the demand for food or in the quantity of food ingested, but in a more or less complete loss of the normal ability to derive energy from carbohydrate food, and a consequent necessity for the vicarious assumption by the protein and fat of the role in producing energy normally taken by the carbohydrates.

It has always been known that diabetics hunger and emaciate; it has also long been known that a diabetic practically always excretes much more nitrogen than a normal man. The first impression that these facts give is that there is some essential factor in the disease which causes abnormal activity of tissue destruction, and that the excess in nitrogen excretion is direct evidence of excessively active protein metabolism. It was taught for many years by authorities that an essential feature of the disease was azoturia, and that the nitrogen excretion regularly exceeds the intake; and, indeed, the same statement is still often made or im-

plied. As regards the fats, too, it may usually be observed that the loss in weight is more than the nitrogen loss will explain, and it is known that a diabetic early loses practically all his reserve store of carbohydrates. The conclusion is, therefore, justified that the man is losing fat, and his tissues themselves show this. Hence, wasting of the fatty tissues is often accepted as an essential part of the disease. In neither instance, however, is such a conclusion justified. The losses of fat and of nitrogenous tissues may be shown to be, in ordinary cases, purely secondary and due to the fact that the subject of the disease, though taking large amounts of food, is excreting so much of it practically unchanged that he is actually using for the production of energy an amount which is decidedly below the demand. The continuance of the demand for energy necessitates a proper supply, however, and the protein tissues and fat are broken down in order that they may yield this energy and not because their functions are abnormal. The unusual appetite exhibited by a diabetic is then a really normal appetite in that his tissues show no abnormal excitation of their food demands. Large amounts of food must be ingested merely because much of the food is wasted; and the subject emaciates only because he does not, as a rule, take a sufficient amount of the proper kind of food, *i. e.*, the kind that he can use; his supply of energy is below the demand, and his body protein and fat must fill the gap as far as possible. To appreciate the correctness of this view and the fact that the contrary teaching is erroneous, one must remember certain facts relating especially to the metabolism of the proteins in a healthy subject when the food supply is normal and when too little or too much food is given. There is not a sufficient general understanding of certain well-established facts which are all-important in this relation. In the first place, it should be more generally recognized that under normal circumstances the excretion of nitrogen is regulated almost entirely by the character and amount of food that a man takes and not by his manner of life as regards exercise, etc. If a mixed diet of proper quantity be given a normal man his tissues will in a very short time, usually a very few days, accustom themselves to the diet, and it may then be seen that whatever the amount of protein contained therein, his nitrogen excretion during a given period will be

equivalent to the amount of nitrogenous food he absorbed during that period; in other words, that he maintains a nitrogen balance. It is necessary only to see that the total value of his food in units of energy is sufficient to meet the demands for energy, and that the daily ration does contain a certain amount of protein. The active tissues of the body are nitrogenous, and their activity means a certain amount of wear and tear, and consequently some protein is necessary to replace the loss. But this loss is small, and the protein may be reduced to as low as 30 to 50 grams a day without causing any loss of body protein during an extended experiment. Even active muscular exercise causes practically no increase in the nitrogen excretion if only the other foods are increased so that the total intake meets the increased demand; and a reduction of exercise, while the protein is still given in large amounts, does not cause any distinct reduction in the nitrogen excretion, though it may cause the subject to grow fat. If food is given in very large amounts, more than necessary for the body needs, the subject will generally grow fat, but a nitrogen balance is again soon reached even if very large amounts of protein are given. If, however, the food is reduced in total quantity below the amount which is necessitated by the man's expenditure of energy, a loss of nitrogen will be seen at once if the excretion be compared with the intake. This loss will occur even though a relatively large amount of protein is taken. If the man be now given an amount of food which will bring the total food value up to the point demanded by his circumstances, he will reach a nitrogen balance again. The increase in foods need not be in protein, providing the protein has not been reduced below the relatively low limit of absolute demand, for it has been conclusively shown that protein loss can be easily controlled by giving more carbohydrate and, to a less complete and satisfactory extent, by giving fats.

There are a number of conclusions that can be drawn from these facts, which are of importance in connection with diabetes. In the first place, protein is evidently not stored in the body. This conclusion is not wholly justified, as Krug's work seems to show that overfeeding with protein may, under favorable circumstances, cause some storage. His results, however, are justly

questioned, and even if accepted they show extremely slight protein storage (producing only 5 per cent. of the increase in weight as compared with 95 per cent. due to increase in fat), and it is probable that the conditions producing such a storage could not be long maintained. Secondly, the protein both of the food and of the tissues is evidently readily broken down; with a general excess of foods or with an excess of any kind of food, even of protein, the protein is broken down at once, the fats and carbohydrates being stored; while if there be a demand for more food than is given the body-protein practically always suffers. And thirdly, and much more important in direct connection with the question under discussion, it is evident that a negative nitrogen balance, while it may mean excess in the activity of protein metabolism, may mean merely that the subject is taking too little food, all told. In health this is evidently the explanation, and in disease it is the first thing to be thought of. Fourthly, and quite as important in diabetes, it is evident that a nitrogen loss may, with healthy nitrogen metabolism, be converted into a nitrogen balance if more food is given, and that it matters little what form of food is given so long as the protein is not extremely low and the total value in energy units is normal under the circumstances. The possible explanations for the increased nitrogen elimination in diabetes are, therefore, three. It may be due to an increase in the ingestion, to a lack of sufficient food, or to a pathologic essential increase in protein metabolism. The diabetic usually takes enormous quantities of food; hence the first factor evidently explains some of the increase in urinary nitrogen. It is not this alone, however, for the loss exceeds the intake. Of the other two, then, it may, in the ordinary uncomplicated case, be readily shown that a lack of proper food is at fault. A pathologic increase of protein metabolism does sometimes occur in the last stages of diabetes, particularly when the patient is in danger of coma; but under ordinary circumstances, if the total caloric value of the food be calculated, and the loss in the sugar excreted be deducted, it will be found that the diabetic is making use of food only in amounts too small to meet the necessities of the occasion. If now his fats and proteins be increased to such a point that the total food value, after deducting the excreted sugar, is equal to or greater than the

amount he needs, it will be found that the nitrogen balance is normal, and he may even retain nitrogen until the previous loss is replaced. Evidently, then, the protein metabolism is normal. As to the fat, conclusions are much more difficult to reach, except by inference. As has been stated, however, if a diabetic is given sufficient food, with consideration of the sugar loss, he will cease to lose weight, and with more food will gain weight, more even than the protein retention will explain. He tends, therefore, to retain fat and not to destroy it, if given the opportunity by being furnished enough total food, for a carbohydrate retention cannot explain the increase in weight. Further, the intake of oxygen is normal; hence there is no increase of the normal oxidation of fats. There is also no good evidence that fats can contribute largely to the formation of carbohydrates in the body, indeed the most satisfactory evidence points against this; there is, therefore, no opportunity for an indirect increase of fat destruction through contributing to the sugar production and loss. And finally, many cases of diabetes even show a distinct tendency to obesity. There is, therefore, no reason for believing that there is any increase in the oxidation of fats, either direct or indirect, excepting in an attempt to replace a deficit in the food.

But while there is no destruction of fats and protein in diabetes, excepting that which has the normal purpose of supplying the energy demanded, there is an evident disturbance of the metabolism of the carbohydrates, which is most easily seen in the characteristic and generally known symptom, glycosuria. The primary reason for this disturbance is both the most important and the most obscure question in diabetes, but valuable facts concerning the abnormality are known. Normally, we take the carbohydrates of our food chiefly in the form of hexoses—*i. e.*, their molecules contain six atoms of carbon, or a multiple of six. It is now known that our food does contain pentoses in considerable quantities, and that they play some part in our nutrition. It is not improbable that they are of decidedly greater importance in this way than is even now admitted, but they are probably largely transformed into hexoses after their absorption before they are used by the tissues. At present our interest certainly attaches chiefly to the hexoses. These are absorbed largely as glucose,

though to some extent as levulose, and also, in small amounts, as polysaccharids. Absorption takes place into the portal circulation almost exclusively. After this point the changes in the sugar are somewhat uncertain as to the main facts and entirely obscure in many details. It is quite possible that all the sugars, including glucose, pass through the glycogen stage before they are admitted to the general circulation. It is certain, at any rate, that, practically speaking, all the sugar normally admitted to the general circulation is in a form which gives the chemical and physical reactions of glucose, and that normally the amount in the general circulation is kept at a fairly constant but low level, the percentage being about 0.12 or 0.15. Any excess taken as food or formed in the organism is stored in the liver and muscles as glycogen, or if these reservoirs are filled to their limits, is changed into fat and deposited as such. If the supply is low the glycogen reservoirs are called upon and the glycogen is transformed into glucose and furnished to the circulation as such and not as glycogen. The existence of the glycogen reservoirs makes it possible to keep the percentage of sugar in the blood at the normal level in the long periods between meals, and in spite of temporary starvation or other unusual demands; the glycogen lost is soon replaced from a new supply of food, so that the total quantity of glycogen shows only temporary variations and a reserve is always on hand. The sugar admitted to the blood is, practically speaking, entirely used in the economy, the excretions containing only end products of its breakdown. The normal urine does contain a small amount of carbohydrate, and some of this seems to be glucose, but the quantity is too small to be considered of any practical importance.

The alterations in diabetes manifest themselves in all these main points—in the storage of glycogen, in the quantity of sugar in the blood, and in the striking change in excretion. The glycogen becomes reduced in amount and may almost disappear; sugar is found in the blood in abnormal amounts, constituting a so-called hyperglycemia, and more or less of this sugar is excreted in the urine as glucose and the energy contained in it is lost. The characteristic and distinguishing feature of diabetes is that these conditions are not dependent upon temporary causes, but are persistent and usually tend to increase. Any of the changes men-

tioned may occur temporarily as the result of numerous causes. The store of glycogen may be more or less completely reduced by starvation, particularly when associated with active muscular exercise; various nervous insults, particularly the *piqûre* of Claude Bernard, and many general operative procedures will have a similar result, the latter probably acting largely through the nervous shock which they produce. Undoubtedly a hyperglycemia results in most of these instances, except in starvation, from the sudden flooding of the circulation with glucose formed from the glycogen, and hyperglycemia results also in most if not in all of those conditions in which we observe so-called alimentary glycosuria. As to temporary glycosuria, this is a practically inevitable sequel of hyperglycemia, when this reaches any notable degree, and consequently occurs in any of the conditions mentioned in which the percentage of sugar in the blood rises distinctly above the normal. It is in this way that glycosuria may probably be explained when it occurs after trauma, experimental nervous insults, shocks in various diseases (as in gallstones), and in so-called alimentary glycosuria. In some cases a glycosuria is, however, independent of any mere excessive production of glucose from glycogen or of a flooding of the blood with sugar by other means, such as the ingestion of large amounts of sugar. In some poisonings, particularly that produced by phloridzin, there is, without any hyperglycemia, a more or less decided glycosuria. In these instances the glycosuria is evidently not due to increase in the amount of sugar in the circulation, but to either a change in the chemical character of the sugar itself, or a change in the kidney permitting of the passage of the sugar. Infections also may cause glycosuria. They probably act as a rule through the production of a hyperglycemia, though possibly at times by alteration of the sugar or of the kidneys. But while it is possible that all the factors mentioned—poisonings, infections, shocks of various kinds, over-ingestion of carbohydrates (when protracted and particularly when largely of sugars), and even starvation—may cause diabetes, and it is certain that some of these factors do at times produce the disease, the usual characteristic of the changes which they set up is that they are but temporary, and disappear at once when the cause ceases to act, or at most soon afterward. If this is not the case the abnor-



mality is actual diabetes. Of the conditions mentioned the one that most closely approaches diabetes is alimentary glycosuria, when this occurs persistently and after taking only moderate amounts of sugar. A normal person is evidently limited in his power of making immediate use of the carbohydrates which are absorbed from his gastrointestinal tract. Under normal circumstances the sugars absorbed are formed gradually during the process of digestion, and hence are absorbed in only small amounts within a given time. Only small amounts need to be dealt with, therefore, at one time. If, however, a normal person is given readily absorbable sugar in large amounts he absorbs large quantities within a brief period, particularly if his stomach and small intestine are practically empty when the sugar is taken. If the quantity given is large enough, any normal person will react by the excretion of some of the sugar in the urine. The most evident reason for this, and the one generally accepted, is that he is unable to consume or store quickly such large amounts of sugar, his general circulation is flooded with sugar, and his kidneys excrete the excess. In other words, the normal ability to consume or store sugar quickly is limited. It may be observed in a large series of abnormal conditions where there is no actual diabetes, that an alimentary glycosuria may be produced much more readily than normally, *i. e.*, the ingestion of quantities of sugar that are normally fully used in the economy results in glycosuria. Among the prominent conditions in which this occurs may be mentioned neuroses (traumatic and other forms), organic nervous diseases, chronic or acute alcoholism, infectious diseases, pancreatic disease, and exophthalmic goiter. It is found in disease of the liver at times, but not in the large percentage of cases at one time thought. The essential points of distinction between a pure alimentary glycosuria and diabetic glycosuria is that the former occurs only after taking sugars and ceases when the excess is excreted, while the latter occurs after taking carbohydrates in any form, and often even when no carbohydrates are taken, it is more or less constantly present, even under normal conditions of life, and it is persistent and shows a strong tendency to increase. Alimentary glycosuria is present in diabetes, but does not necessarily mean diabetes. When the assimilative power is decidedly low, however, there is a dangerously

close resemblance to diabetes in that in both conditions the normal power of making use of carbohydrates is much reduced ; but in pure alimentary glycosuria the alteration is quantitative only, while in diabetes it is both qualitative and quantitative. One striking difference between alimentary glycosuria and diabetes is that in the former the sugar excreted is practically always purely the kind ingested, while in diabetes the sugar found in the urine is, with very rare exceptions, glucose. But while the sugar excreted in diabetes is nearly always glucose, there is a distinct difference usually seen in the effects of the ingestion of different sugars. While all forms of sugars almost always increase the glycosuria, glucose is always badly tolerated and more or less completely eliminated, and the various polysaccharids are also but poorly borne.

There is, as a rule, some power of using lactose, and levulose is frequently consumed to a very considerable extent, and may even cause an accumulation of glycogen ; the latter point is one of importance in attempting to make the cause of diabetes clear. Besides the effect of the carbohydrates of the food, striking effect may be seen from the food protein and the protein of the body. It is now certainly known that both these forms of protein furnish some carbohydrate normally, though whether it is a mere splitting off of a carbohydrate molecule already present in the protein, or the carbohydrate is formed by a more complex synthetic process after the partial breakdown of the protein molecule, is not known. Normally, this carbohydrate, like that already found as such, is completely used in the economy, but in diabetes it frequently increases the difficulty and is more or less completely excreted. But certainly the carbohydrate formed from protein is more readily assimilated than that taken as carbohydrate, as the exclusion of preformed carbohydrates from the food will frequently cause the glycosuria to cease, and it is only in severe grades of the disease that the carbohydrate formed from protein is excreted in large percentage. Fats do not, from all satisfactory work on the question, seem to increase the glycosuria, or indeed to form sugar at all. Bouchard and Desgrez have claimed recently that they may cause increase of the muscle glycogen, however, and this may possibly prove to be true.

The power of using preformed carbohydrate of any variety is rarely or perhaps never completely lost. Rumpf has recently claimed to have shown its absolute loss, and some other writers agree with him that this may occur, though no conclusive evidence of it has ever been offered. There are a number of cases on record, however, in which the loss was almost complete, and there seems no good reason that absolute loss should not occur at times. There is, however, never an entire loss of the ability to use carbohydrates in general, whether preformed or produced from protein. The possible variations are from the almost complete (or possibly complete) loss of the use of preformed carbohydrates, to a very slight and variable loss. In general there is a tendency for increase in the disability, and if carbohydrates are taken in any considerable amount this tendency is usually increased, often strikingly so. The most rational explanation of this is that the carbohydrate function, already weak, becomes overtaxed and still further reduced if excited to any degree. The abnormality also shows a decided tendency to more or less protracted fluctuations in degree, and may even spontaneously disappear for varying periods. Daily fluctuations are also seen in the sugar excretion, but these are probably due, as a rule, chiefly to the pauses between meals and consequent variations in the amount of sugar absorbed from the gastrointestinal tract.

Turning now from the characteristics of the metabolic disability to its effects—the chief immediate changes which can be determined are, as stated, an accumulation of sugar in the blood, a reduction of the glycogen in the liver, and to a lesser extent of that in the muscles, and a loss of sugar in the urine. The most striking clinical effects are largely secondary to those mentioned; they are chiefly hunger, emaciation, thirst, and polyuria. The hunger and emaciation are, as previously stated, evidently due to food loss through the excretion of sugar in the urine. They are the result of the fact that while the subject of diabetes takes a normal amount of what to a normal man is useful food, a very considerable portion of this is actually not food to the diabetic and cannot be used as such, and is excreted practically untouched. Hence he provides his tissues with an abnormally small amount of the substances which they can use as food. The hunger and

emaciation are then their expression of a lack of sufficient food. An explanation of the thirst is usually simple enough. It is entirely or almost entirely dependent upon the polyuria; the loss of water, in the excessive excretion through the kidneys, makes the tissues poor in fluid, and the symptomatic expression of this is thirst. The polyuria is not quite so readily explained. It is certainly in chief part and in most cases explainable through the existence of a hyperglycemia. The kidneys are so constituted that they will not allow of the passage of sugar unless it be present in the blood in abnormal amounts. When it is present in abnormal amounts, however, the kidneys practically always make an attempt to excrete the excess. The sugar passes the kidneys in solution, and for the solution of large amounts of sugar, large quantities of water are necessary, hence polyuria is an almost inevitable accompaniment of glycosuria.

The fact that the kidneys allow the sugar to pass when it is present in the blood in excessive amounts is commonly spoken of as if it were an overtaxing of the kidneys, and the glycosuria is apparently usually thought of as an unfortunate occurrence. It is, of course, generally recognized that the glycosuria is not of itself the cause of symptoms, but is the expression of some abnormality further back in metabolism; but it should be recognized also that instead of being a misfortune in itself, the excretion of sugar through the kidneys in hyperglycemia may be looked upon as a happy event; it must be largely an altruistic and purposeful act of the kidneys rather than the mere expression of a limit of power in retaining sugar. Hyperglycemia is an unfortunate condition in many ways, and were there no attempt on the part of the kidneys to reduce the excess of blood-sugar so far as possible, the results upon the tissues of the mere hyperglycemia itself would probably soon become grave in nearly all cases of diabetes. These results of hyperglycemia are among the most important of the secondary effects of the metabolic disturbance. They consist chiefly in a striking tendency to infection and necrosis of the tissues. It is generally known that the subjects of diabetes have a very marked tendency to pyemia, to tuberculosis in particular, to sepsis, to gangrene, and to many other infections. The gangrene can be explained to a considerable extent through the arteriosclerosis; but

considering the strong tendency that diabetics show to other forms of infection, it is rash to follow the recent tendency of some surgeons and medical clinicians, and to attribute the liability to gangrene almost exclusively to the arteriosclerosis that is often present. As to the tendency to tuberculosis, to pyogenic sepsis, and to many other infections, there is fairly general acceptance of the idea that these are largely due to the hyperglycemia. The existence of an excess of sugar in the blood and other body fluids makes this a much more favorable culture medium for bacteria, and it is perfectly reasonable to consider that the peculiar liability of diabetics to infection is largely due to this alteration of the body fluids. There are two other factors which must be considered, however. A diabetic is often an extremely ill-nourished person, and his very severe reduction of nutrition certainly favors infection, as infection is favored in other conditions of malnutrition. The third possible cause has recently been insisted upon by Teissier, who found that the presence of glycogen in culture tubes largely or completely hindered the growth of various forms of bacteria. He considers these observations added testimony of the correctness of the view previously expressed by Roger and Amato that the reduction of the glycogen of the liver so commonly seen in diabetes favors infection by reducing the bactericidal power of the liver. This is a somewhat theoretic explanation which may have considerable truth in it, but the actual knowledge of the role played by the liver in the prevention of infections is not yet sufficiently accurate to base ideas chiefly upon that supposed function of this organ, and it is certainly not yet sufficiently proved that the glycogen in the liver prevents bacterial growth and activity. The hyperglycemia is almost certainly the most important factor in favoring infection; one fact which seems to make this very definitely evident is that v. Mering and Minkowski in their original communication on experimental pancreatic diabetes strongly emphasized the tendency exhibited by the animals experimented upon to acquire infection almost at once. This infection usually took place locally through the wound made in operating, and this seems much more like local infection due to a proper condition of the body tissues and fluids than a tendency to general infection through reduction of the bactericidal power of the liver; the ten-

dency to infection was also so rapidly developed in these animals that the reduction in nutrition does not seem to have played a very important role. In closing this portion of the subject it may be mentioned that it is claimed that diabetes is demonstrable by observing the reaction of the blood to dyes, particularly to methylene-blue. These reactions probably depend almost exclusively upon the existence of hyperglycemia. The tests which have been used in this connection are those of Bremer and Williamson. Bremer has two reactions: One of them consisting in a peculiar behavior of diabetic urine to stains; the other in alterations in the staining reactions of diabetic blood. Williamson's test consists in a rapid decolorization of a weak alkaline methylene-blue solution when diabetic blood is added to it. Investigation of Bremer's reactions has shown, as might have been postulated without special study, that while they are almost always positive in diabetes, when hyperglycemia and glycosuria are marked, there are other conditions of the blood and urine that may give an apparent reaction, and there are also so many possibilities of error in the technic of the preparation of the blood that this reaction is of no serious consequence in actual diagnosis. As to Williamson's test, it is, in the first place, necessary to carry out the reaction with the utmost care as to details, and errors in technic are very likely to occur. Furthermore, the only instances in which the reaction is likely to be of any real value are in cases in which there is no opportunity to determine the existence of glycosuria, for glycosuria, if present, is a sign which is much more readily and certainly demonstrated. Such conditions are probably at most two. One of them is the absence of glycosuria, while hyperglycemia is present. If such a condition exists it is extremely rare, and even if the possibility of its occurrence be admitted, certainly hyperglycemia can be present in only extremely slight degree without a coexistent glycosuria, and it is questionable whether a very slight degree of hyperglycemia could be determined by this rough test; probably it could not. The condition in which Williamson thinks the test is more likely to give useful results is in diabetic coma, when urine cannot be obtained for examination, and when one desires immediate security in his diagnosis. A negative result, however, under such conditions, could never be depended upon as indicating the absence

of diabetes, as it is well known that preceding or during coma, glycosuria and hyperglycemia not very infrequently disappear more or less completely. For this reason alone it is probable that Williamson's test would be negative in a certain proportion of cases of diabetic coma, if glycosuria were absent. There are instances in which the bladder contains no urine, and yet glycosuria and hyperglycemia are present. In these extremely rare cases Williamson's test might be of value. It must be remembered, however, that up to the present the test has not been well studied in relation to the other conditions which might possibly give a reaction. From some investigations that have been made it appears that the reaction, or something practically undistinguishable from it, may occasionally appear in other conditions. It would seem, therefore, that the possibilities of a negative result in actual diabetes and of a positive result in other conditions make the test so far unreliable that it is a very insecure basis of diagnosis. The proper observation of the symptoms, together with the investigation of the urine, if this is possible, and the discovery in it of large amounts of acetone, diacetic acid, and perhaps of  $\beta$ -oxybutyric acid, afford much more satisfactory and far more reliable methods of diagnosing diabetic coma.

The discussion of metabolism in diabetes would, of course, be incomplete without a mention of the conditions in coma; but the questions arising in connection with this complication are so intricate and have given rise to such extensive discussion that only the most notable points and those which seem fairly well established can be given. So far as nitrogen metabolism has been studied, it seems, while somewhat variable, to be very likely to suffer an abnormal excitation with the approach of coma. The subject of the disease, while previously in nitrogen equilibrium if properly fed, often shows with approaching coma a loss of nitrogen which cannot be replaced by increasing the protein food within safe limits. The cause of this increase in metabolism is not clearly evident, though it is certainly an expression of toxemia. With the nitrogen loss the patient commonly suffers a loss of fat. The carbohydrate disturbance usually continues, and at the period when coma is approaching, has generally become of severe degree. One striking point, however, which is always worthy of being remembered,

is that, as previously noted, in some cases the sugar excretion disappears as coma approaches and during the course of coma. This is perhaps due chiefly to reduction in the amount of food taken, and a consequent reduction in the amount of carbohydrates supplied to the circulation, though this is by no means a complete and satisfactory explanation. But the most notable facts about diabetic coma, so far as one is directly concerned with questions of metabolism, are the evidences of intoxication that precede or accompany the coma. The facts best known to the clinician are that acetone and diacetic acid are found in the urine in more or less considerable amounts. It has also been shown chemically, and is evident upon mere observation, that acetone is given off in large quantities from the lungs. Acetone is known to be toxic, and it was long taught, and is still widely believed, that diabetic coma is actually an intoxication with acetone. It has, however, been shown satisfactorily that acetone, while it may and probably does play some part in the production of coma, is far from being the sole or even the chief cause of the coma. Acetone is really an end product of the acids which cause the coma rather than itself the cause; and although acetone may readily be conceived of as contributing to the production of intoxication, it cannot be considered to be chiefly active in causing the peculiar symptoms seen in diabetic coma. In the first place, acetone is but mildly poisonous, and when given to man or animals, even in the amounts excreted during the course of diabetic coma, produces only mild symptoms, if indeed it causes any; also, the amount excreted shows no regular parallelism with the progress of the intoxication; and further, the symptoms produced by poisonous doses are not those of diabetic coma. It may properly be said, also, that it has never been quite conclusively proved that acetone is ever found in large amounts in the body, and a number of observers contend that all the acetone found in the urine is excreted as diacetic acid, and that this is subsequently oxidized to acetone. This view is probably not correct; the reasons given are sufficient, however, to show that acetone cannot be considered to be the cause of the peculiar coma. But a further and still better reason is found in the fact that other substances are present in diabetic coma and preceding its onset, which show a close and almost con-



stant relation to the symptoms, and which may from analogy with the results of experiments be fairly considered to be the cause of the coma. It is now well known that preceding and during coma there is so large a production of acids as to flood the blood and tissues with these, and to cause the excretion of large amounts of alkalies combined with the excess of acid. It is also well known to experimenters that administering large amounts of acids of various kinds will result in the appearance of a condition which resembles diabetic coma in several of its most distinctive features. Somewhat similar symptoms of intoxication may also be produced by giving to animals large quantities of those forms of food which will produce acids in large amount in the process of the breakdown of the food, providing that the animals are not accustomed to such a method of feeding.

The most satisfactory explanation of typical coma then, so far as our present knowledge goes, is to consider it a form of intense acid intoxication, due not to any special toxic agent, in its typical form, but to the mere excess of acid, and to the consequent reduction of the alkalies of the blood and tissues through their neutralization by the acid. The substance which is undoubtedly chiefly active in the production of the intoxication is  $\beta$ -oxybutyric acid. This has been shown, since the work of Minkowski and Külz first demonstrated that it may be found in this condition, to be present in large quantities during coma or preceding its onset in the great majority of cases. It has not any severe toxic action which is peculiar to itself; it is, however, present in such large quantities as to be capable of producing acid intoxication through its action simply as an acid. Diacetic acid is also found in large amounts when coma is imminent or present; it is very probably derived from the  $\beta$ -oxybutyric acid, though it is possibly separately produced. It is almost devoid of any special toxic properties, and is active in the production of diabetic coma only through its acid properties, but it is almost certainly present in sufficient amounts in many cases to aid, at least, in the production of the acid intoxication; it is impossible to state this absolutely, since the amount of diacetic acid cannot be satisfactorily determined quantitatively.  $\beta$ -oxybutyric acid is, however, present in much larger amounts and is of itself somewhat toxic; it is certainly much the more

prominent factor in the production of the coma. Acetone is a derivative of  $\beta$ -oxybutyric acid and diacetic acid, and is therefore chiefly the expression of the conditions causing the coma rather than itself the cause, though, as previously stated, its toxicity is sufficient to make it probable that it aids in the production of intoxication, though not directly in the production of the peculiar symptoms of diabetic coma. There has recently been an attempt to demonstrate the possibility that diabetic coma is due to a substance which has a special toxic effect, and which through this latter action produces the special symptoms of diabetic coma. Sternberg, assuming that  $\beta$ -amidobutyric acid might be present in diabetic coma, has investigated the effect of this acid upon animals, and claims to have produced with it a condition practically identical with the peculiar coma of diabetes, and Grube states that he has confirmed Sternberg's results. Magnus-Levy very properly objects to the acceptance of these results, however, upon the ground that the amido-acids found in the human organism are of the alpha, not the beta, series, and that the theoretic assumption of the existence of  $\beta$ -amidobutyric acid is unjustified. There is also question whether the conditions produced were really those seen in diabetic coma. While it may be true that some special toxic agent produces the peculiar symptoms, this does not, from our present knowledge, seem at all essential. The conditions in true diabetic coma vary to a certain degree, and other acids besides  $\beta$ -oxybutyric and diacetic acids (lactic, volatile fatty acids, etc.) have been demonstrated to be present in large amounts in some instances, and were very possibly the cause of the coma in these cases; hence coma seems to be produced by a flooding with acids of various kinds. Also a condition practically indistinguishable from diabetic coma has been observed in a number of other diseases, such as carcinoma and pernicious anemia, when there was evidence of profound acid intoxication. These facts, together with the observation of experimenters that various kinds of acids produce a similar condition when the amount given is large enough, demonstrate with a considerable degree of certainty that the coma is at least in chief part due to the action of the acids as such, and not to any special toxic substance.

The source of the acids has been a matter of great controversy.

It is demonstrated by both experimental work and by clinical observation that the use of carbohydrate food not only does not produce these acids, but tends to decrease any existing acid intoxication. It has until recently been very generally accepted that the acid intoxication is produced by the breaking down of protein. It is well known that the destruction of protein produces considerable quantities of acid, and one of the most striking reasons for accepting this source of the poisoning is that when acid intoxication occurs the subject is usually losing large quantities of nitrogen in spite of the large intake, and is therefore breaking down large quantities of the protein of the body tissues as well as of the food. It has, however, not been satisfactorily established that  $\beta$ -oxybutyric acid, diacetic acid, or acetone can be produced from protein, though the recent work of Blumenthal and Neuberg makes it seem probable that this may actually be accomplished in the human organism as well as artificially. Their work, however, is not yet confirmed. In the absence of thorough proof of production of these substances from protein, and in the very satisfactory demonstration, by Geelmuyden and Magnus-Levy in particular, that they may be produced from fats, the belief has become quite generally accepted that the fats of the food or the body, or of both, are probably the source of the acids producing the intoxication. One must at present, therefore, consider the source of these acids to be chiefly the fats; though it is highly probable that the protein also contributes to their production, and it must be accepted as practically certain that proteins at any rate contribute to the acid intoxication through the production of other acids, since the breaking down of protein food always produces a considerable amount of acid. It has been very definitely demonstrated by both clinical observation and experiment that the acid intoxication occurring in diabetes may be due to the use of a protein-fat diet, or to breaking down of similar body tissues. A complete or almost complete restriction of carbohydrates from the food is very likely to be followed by the appearance of acetone and diacetic acid in the urine in diabetes, as is well known to clinicians, and the experiments of Gerhardt and Schlesinger show that a similar result may be produced in normal persons; and the substitution of carbohydrates for some of the protein and fat fre-

quently causes the disappearance of the acetone and the diacetic and oxybutyric acids and of the symptoms of approaching coma if they were present. In what way the carbohydrates exert this action is not fully understood, as such an effect may sometimes be seen when comparatively little carbohydrate is given. It seems probable that the carbohydrates in some way influence the metabolism of the protein and fat, besides reducing the quantity of the latter which it is necessary to give.

While the appearance of large quantities of acetone, and more particularly of diacetic acid, in the urine furnishes what must continue to be the best general clinical index of the danger of the onset of coma, a more exact method of determining the degree of acid intoxication and its progress is by estimating the ammonia of the urine; one may practically always see that with increasing acid intoxication the ammonia excretion in the urine coincidentally increases, and in most cases this increase is practically proportionate to the degree of intoxication with acids. The reason for this is that the acids produced in the body are normally neutralized largely by the fixed alkalies, only small amounts of ammonia being excreted. If, however, the amount of acid to be neutralized becomes much larger than the normal, the fixed alkalies do not suffice to neutralize the acids or they cannot be so largely used without causing a dangerous reduction of the amount remaining in the body fluids. Under such circumstances, according to the teaching of the Schmiedeberg school, which is the most satisfactory, the ammonia formed in the body, instead of being excreted as urea, unites so far as necessary with the acids and is excreted in combination with them.

An interesting fact which has been well shown recently by Gerhardt and Schlesinger, and has previously been indicated by the work of others, is that the excretion of calcium and magnesium, particularly of the former, is increased during the acid intoxication, and there may even be a decided calcium loss which may be controlled to a considerable extent by modifying the diet or by giving alkalies. This fact is of great abstract interest, and it is wholly probable that it may have a good deal of actual clinical importance. The calcium salts play an extremely important role in organic chemistry in numerous ways, one of the most impor-

tant of which, in animal physiology, is their influence upon coagulation of the blood. An influence similar to that just mentioned is exerted by calcium salts upon the action of other ferments than the fibrin ferment, and it seems not at all impossible that reduction of the calcium salts in acid intoxication may have an important relation to the symptoms produced during such intoxication. The results of metabolic experiments make it wholly worth while to investigate more thoroughly the effects of calcium upon the disease, particularly when there are evidences of acid intoxication.

In conclusion, the main theories concerning the definite nature of the disturbance of metabolism that produces diabetes may be mentioned. These are that the disease is due to overproduction of sugar; that it is due to imperfect oxidation of sugar and its consequent accumulation; that it is due to insufficiency in the production of glycogen so that the sugars absorbed from the digestive tract or formed in the body constantly reach the circulation at once, and the excess, instead of being stored, is constantly being excreted; and that some special toxic agent is the primary cause. The first and last theories at present deserve little consideration. There has never been any proof offered that there is an overproduction of sugar; indeed, the testimony is wholly against such a belief. The whole amount of sugar excreted is never continuously greater than the amount absorbed, plus the amount that we know can be produced from the food-protein and body-protein which are being destroyed at the time. The theory of a special diabetic toxemia, which has recently been put forth by Leo, is based upon inconclusive experiments, which amount to nothing more than the production of glycosuria in a small number of dogs by injecting the urine of diabetic subjects. Urine from other diabetics did not give the same results, and there was no demonstration that actual diabetes occurred in the animals, or that a special toxic agent caused the glycosuria. The choice lies between the other theories—the disease seems to be either a loss of the normal power of destroying the sugars, or a lack of the normal power of producing glycogen, and of controlling thereby the amount of sugar supplied to the blood. Either of these theories would satisfactorily explain the facts observed in most instances.

The general tendency, more particularly of the v. Noorden school, is to put faith in the theory of imperfect oxidation of the sugars. The most important point upon which such a belief is based is that the respiratory quotient (the amount of  $\text{CO}_2$  given off in respiration divided by the amount of O inspired) is low in diabetes. Under normal circumstances the oxidation of carbohydrates in large amounts increases this quotient, while when the amount of fats being oxidized is relatively high the quotient decreases. It would seem, therefore, that in diabetics the amount of oxidization of carbohydrates is below the normal.

This is serious testimony, but it is based upon a very small number of observations, and hence the influence of chance factors cannot well be excluded; and against such results may be adduced the fact that oxidative processes in general are certainly not reduced in diabetes, as it has been shown that many substances which are difficult of oxidation may be oxidized in large amounts by the organism of the diabetic. Further, under ordinary circumstances levulose and glucose are oxidized with about the same facility, but in diabetes levulose is assimilated but glucose is not. This points against suboxidation as the cause. Chauveau and Kauffman also found that comparing the venous and arterial bloods of the diabetic with those of the normal subject there was evidence of oxidation of the sugars in the diabetic subject as well as in the normal one. Their methods were subject to question, however. The work that has been done on glycolysis has not demonstrated anything clearly, unless it be, as Biernacki has recently claimed, that glycolysis is very variable in diabetes; Lépine's attempts, and those of others, to demonstrate the absence of the glycolytic ferment or reduction in its activity have not been successful, and his suggestion of a loss of glycolytic action of the body fluids in diabetes is, therefore, not at all supported by experimental work. The theory of imperfect glycogen production is suggested by a number of facts, the most important of which is perhaps the observation that levulose is frequently made use of in large amounts by the diabetic organism when glucose is largely or completely excreted unused; and more particularly that levulose will frequently produce an accumulation of glycogen in the liver while glucose will not. This would seem to indicate that it

is impossible in diabetes to produce glycogen from glucose, while this occurs normally with levulose. It seems improbable when viewed in this connection that the oxidation of glucose is at fault, because the levulose after producing glycogen in the liver is normally furnished to the circulation in the form of glucose; in spite of this it is largely or completely oxidized thereafter, apparently even by the diabetic in many instances. Further testimony of the possible correctness of this view has been recently furnished by the results of Sachs, who found that extirpation of the liver in frogs did not alter the power of these animals to assimilate glucose, but did produce a strong tendency to alimentary levulosuria. He uses these results as testimony of the lack of importance of the liver in the production of diabetes; but since, as has been repeatedly stated, levulose is often satisfactorily assimilated by the diabetic while glucose is not, and since extirpation of the liver produces exactly the contrary conditions to those seen in diabetics, these results would seem to indicate also that if levulose passes the stage of glycogen production in the liver, it is properly used by the organism, and that the reason that levulose is well assimilated in diabetes is that there is still power of transforming it to glycogen while glucose cannot be so transformed.

*January 24, 1901.*

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### The Pathology of Diabetes.

SIMON FLEXNER, M.D.

In responding to your kind invitation to prepare a brief paper on this subject I shall not endeavor to cover the entire history of the pathology of this interesting disease. Diabetes, like not a few other obscure diseases, has received such brilliant illumination within the past few years, through experimental researches, that our knowledge has grown with great rapidity and rendered intelligible many isolated observations in human beings on the coincidence of organic changes, especially of the pancreas, with diabetes. Although the pancreas has been shown to influence and regulate carbohydrate metabolism, it is by no means proven that the cause of diabetes is always resident within that organ. I shall ask your

attention to a brief statement of our knowledge concerning pancreatic diabetes and of such evidence as we possess bearing on the influence of other organs or distinct pathologic conditions in the production of that disease.

In the year 1788 Cowley published a carefully studied case of severe diabetes with pancreatic calculus and atrophy of the gland. Other reports, of a later date, were made by Bright, Lloyd, and Elliotson. Bouchardat (1851) would seem to have been the first writer to have connected definitely disease of the pancreas with diabetes. Lancéreaux (1877) drew especial attention to this relation. He was followed by Lapierre (1879) and Baumel (1882), but since that time the literature on this subject has grown rapidly. The experimental contributions to the functions of the pancreas, except in so far as its intestinal secretion is concerned, had yielded no remarkable results until von Mering and Minkowski's publication on the effects of complete extirpation of the gland in the dog (1889), although Haller had already stated that it was followed by increased hunger and thirst. Claude Bernard showed that tying off the duct of Wirsung produced no effect, and Schiff, who injected fat into the ducts, saw the gland atrophy, but apparently without causing diabetes.

Extirpation of the pancreas in the dog causes, without exception, diabetes of severe grade. The elimination of sugar by the urine reaches 10 per cent. or more; the animals, notwithstanding their ravenous appetites, lose weight and flesh; they exhibit pronounced thirst, and ultimately become very weak, and succumb. Complete extirpation of the gland in cats, rabbits, swine, toads, and frogs is followed by similar results. In birds, removal of the pancreas gives rise to diabetes, but without causing a constant glycosuria. The blood, on the other hand, as has been shown by Weintraud and Kausch, shows a considerable increase in its sugar content (hyperglycemia).

Dogs, after extirpation has been practised, may begin to secrete sugar from the kidneys as early as six hours after the operation; but even at the end of twenty-four hours the amount does not usually exceed 1 per cent., although 5 per cent. has been noted. On the second day the amount exceeds 5 per cent.; on the third day it reaches 8 to 10 per cent. The maximum would appear to be



22 per cent. (Hèdon, with bread diet) and 16 per cent. (Schabad). The high percentages are maintained until toward the end, but finally, and when the emaciation has become very great, the quantity is diminished. As the sugar falls to the minimum, acetic acid, acetone, and oxybutyric acid appear in the urine (von Mering and Minkowski). The acme of the secretion of sugar is reached from carbohydrate food; but a pure albuminous diet does not reduce the amount below 5 to 6 per cent., while fasting for a period of seven days does not suffice to cause its entire disappearance (von Mering and Minkowski). Incomplete removal of the pancreas is not necessarily followed by diabetes—one-fifth of the gland left either *in situ* or transplanted beneath the skin may avert it. Should the amount left behind sink to one-eighth or one-twelfth, or should a larger remnant suffer later in its nutrition and undergo atrophic change, a mild form of diabetes arises, which, however, tends, through progressive degenerative changes in the gland, to become more severe, and to terminate fatally.

The voided sugar is glucose. Grape sugar when fed is almost completely excreted as such. Saccharose, maltose, lactose, levulose, and galactose are eliminated chiefly as dextrose. Traces of levulose and galactose appear, however, in the urine.

The amount of sugar present in the blood is increased after extirpation of the pancreas. Hyperglycemia goes hand-in-hand with glycosuria. The former is demonstrable four hours after ablation, and reaches its height in twenty-four hours (Lépine). Toward the end of the disease, when the glycosuria diminishes, the hyperglycemia also falls.

Diabetes, the result of total extirpation of the pancreas, is fatal. No other organ can act vicariously in regulating the carbohydrate metabolism of the body. Hence the function of the pancreas, the disturbance of which produces diabetes, may be regarded in Minkowski's sense as specific. This is not, however, equivalent to saying that the pancreas is the only organ the disturbance of whose functions is capable of producing diabetes. It is probable that other organs also preside over the carbohydrate metabolism, although perhaps in a less degree, and that the pancreas may act vicariously for them, although they themselves have not the power to be substituted for the pancreas (Naunyn). Reale and Minkowski

have shown that the removal of all the salivary glands in the dog is followed by a transient glycosuria reaching 3 per cent. of sugar.

There are no records of complete removal of the pancreas in human beings. Partial resections of the gland have been followed by glycosuria (Zweifel) or diabetes (Hahn, Körte, Krönig, and Bull). In the latter cases the interval between the operation and appearance of the symptoms was as great as one and three-fourth years, and the result may have depended upon a progressive degeneration. That the pancreas in human beings shows marked pathologic changes in cases of diabetes is shown by numerous observations. Windle examined the pancreas in 139 cases of diabetes, and found it normal in only 65; Frerichs found it normal 28 times and atrophic 12 times in 40 cases of disease. Seegen found among 92 cases of diabetes autopsied at the Vienna Pathological Institute, 17 in which there was pancreatic disease. Dieckhoff examined 19 cases of disease of the pancreas, and of these patients 7 were diabetic. Hansemann found among the protocols of the Berlin Pathological Institute, tabulated for ten years, 8 cases of diabetes without pancreatic disease, 6 cases in which no reference is made to the condition of the pancreas; 40 cases in which pancreatic disease and diabetes were associated, and 19 cases in which there was pancreatic disease without diabetes. The 40 cases of pancreatic disease and diabetes consisted of 36 instances of simple atrophy, 3 of fibrous induration, and 1 of a complex nature. Hale White found, in the autopsy records of Guy's Hospital (1883-94) 99 examples of disease of the pancreas. Of these, 16 were instances of atrophy, in 13 of which diabetes had existed. Naunyn, on the other hand, in 40 autopsies on cases of diabetes, saw only 1 in which he considered the pancreas to be the cause of the disease.

Of the causes of the pathologic changes in the pancreas which produce diabetes, the chief one is supplied by concrements in the ducts. Of the 72 cases in the bibliography, 14 were due to pancreatic calculi (Hansemann). Naunyn's case was of this nature. The pancreatic changes consist of secondary atrophy. Next in frequency come the primary atrophies, fibrous indurations, and instances of interstitial lipomatosis. Attention should be paid to another possible explanation of pancreatic atrophy—namely, a cachectic condition which may be the result and not the cause of

diabetes (Friedreich, Naunyn). Hansemann has undertaken to distinguish between the two forms of pancreatic atrophy. In the cachectic form the organ is cylindric and sharply demarcated from its surroundings. Microscopically, the stroma and glandular cells are uniformly atrophic. In diabetic atrophy there is interstitial pancreatitis; on account of adhesions the gland is with difficulty separated from its surroundings and presents a brownish coloration (although it is not pigmented), is of a smoother texture, and microscopically shows hypertrophy of the stroma and atrophy of the secreting cells. But that such examples of interstitial pancreatitis need not invariably be associated with diabetes, the two cases of Obici prove. Hansemann has seen diabetes in an early case of interstitial pancreatitis, and is of the belief that a particular form of pancreatitis, which he calls granular atrophy, is always associated with diabetes. Hanot has described cases of bronzed diabetes (*diabète bronzé*) in which, besides pancreatic disease, hypertrophic cirrhosis of the liver has been present. Twenty-four cases of the disease, all in males, have been collected by Anschütz. Opie, who has reported a case, says: "Clinically, the picture is one of a rapidly fatal diabetes mellitus associated with cirrhosis of the liver, usually of the hypertrophic variety. Bronzing of the skin is not constant, but has been present in the majority of the cases. At autopsy has been found a deep pigmentation of the liver and pancreas, associated with cirrhosis and interstitial pancreatitis." Opie has recently described an instance of diabetes in which the lesions of the pancreas were limited to the islands of Langerhans, which showed hyaline degeneration.

Although the evidence is not complete and unmistakable, yet it must be regarded as proving that the pancreas in man, as in animals, is intimately concerned in regulating the carbohydrate metabolism of the organism, and that a failure of the functioning of the organ in man—analogous to total extirpation in animals—is followed by symptoms of diabetes. That this failure is independent of the digestive function is proved by the results of ligature and occlusion of the ducts, and that it depends upon an internal secretion supplied by the pancreas to the blood is highly probable. Whether this hypothetic secretion is the product of the cells of the islands of Langerhans is unproven. Should future study prove

this view to be true (and the possibility is strengthened by Opie's observation of hyaline necroses of the islands in diabetes without other pancreatic changes), a closer differentiation of pancreatic disease than exists at present will be rendered necessary, and in this light the discrepancies in the relation of diabetes and pancreatic disease, now impossible of explanation, may receive their solution.

The search for the cause of pancreatic diabetes has given rise to much ingenious speculation and numerous experiments. Thus far no satisfactory theory has been advanced, nor have the views put forward found support in experiment. Von Mering and Minkowski proposed two alternatives: (1) There takes place after extirpation of the pancreas an abnormal accumulation of injurious substances which it is the function of the gland to destroy; or (2) an important and irremediable function in the regulation of the carbohydrate metabolism is abolished by the removal of the pancreas. The former alternative was abandoned by Minkowski himself in later writings. The latter still has the greatest number of adherents, although it possesses a purely hypothetic basis; its adoption would bring the pancreas into line with other organs—*e. g.*, thyroid gland and adrenals, which secrete internally, or exhibit, according to Hansemann, a positive function. The manner of the regulatory mechanism of the internal secretion is differently conceived of by different writers. Lépine has concluded, upon an experimental basis, that the normal pancreas contains a glycolytic ferment, which finds its way into the lymph and blood, where it is contained within the white blood-corpuscles. This ferment controls the consumption of sugar by the tissues. Its absence is followed by hyperglycemia and diabetes. The existence of the hypothetic ferment has not been rendered more probable by the results of subsequent experiments, carried out by a number of investigators, and the occurrence of a specific glycolytic power by the blood has, indeed, been rendered highly doubtful. Chauveau and Kaufmann have proposed the opposite thesis. In opposition to the view that diabetes results from diminished sugar destruction, they have set up the theory that it depends upon increased sugar production by the liver. In respect to this function they regard the liver and pancreas as closely related and mutually dependent organs. The pancreas regulates, through the nervous

system, the production of sugar by the liver. The inhibitory center is located in the medulla oblongata, and the center of irritation is in the upper cervical region of the spinal cord. The pancreas acts upon the centers in opposite ways. The "nervous" theory, however, was not wholly confirmed by further experiments, and Kaufmann, in a later paper, admits a partial direct influence of the pancreas upon the functions of the liver. Minkowski is certain that in experimental pancreatic diabetes the fault is not increased sugar production, but disturbance of consumption. The brothers Cavazzani would explain diabetes following extirpation of the pancreas as brought about by consequent alterations of the liver. Experiments have shown that irritation of the celiac plexus causes an increase of sugar in the hepatic blood. A similar irritation may follow removal of the pancreas. Hence an overplus of sugar is produced in the liver, the metabolism of that organ is increased, and degenerations result. This theory is scarcely tenable in view of the effects of the transplantation of the pancreas. Thus far none of the theories advanced suffices to explain all of the phenomena observed. What appears to be beyond doubt is that diabetes results from the failure of a special internal function of the pancreas, and that it is not due to nerve lesions or to the absence of the digestive secretion of the pancreas.

That diabetes can also result from disease of the liver, the pancreas remaining normal, seems probable. Glycosuria is more common as a result of hepatic disturbance than diabetes, and arises commonly after occlusion, temporary or permanent, of the common bile duct. The suffusion of the liver with bile brings about the excretion of the stored-up glycogen, so that no further quantity is obtainable after Claude Bernard's *piqûre* (Wickham-Legg, and others). Traumatism of the liver has also been cited as a cause of diabetes, but upon very insufficient evidence. On the other hand, diabetes has been observed as an accompaniment of cirrhosis, and in several such instances reported by Naunyn the pancreas has shown no pathologic changes, even upon microscopic examination, and similar examples of diabetes in the course of chronic vascular and cardiac disease, in which the liver has suffered congestion, have been recorded.

The proof of the hepatic origin of diabetes is inconclusive, and rests upon far more insecure grounds than that of the pancreatic origin. Experimental support for the former is almost entirely wanting, and the major cases in human pathology do not exclude concomitant involvement of the pancreas. The close anatomic relationship which exists between the vascular supply of the pancreas and liver produces unavoidably common pathologic disturbances, such as would be felt especially in cirrhosis and chronic congestion. Moreover, our knowledge of the extent of pancreatic disease, and perhaps even the kind of disturbance of function with which diabetes is associated, is too imperfect to permit of the total exclusion of the pancreas, even in the absence of moderately severe microscopic lesions. What is established is that in certain chronic pathologic conditions of the liver, the pancreas being without demonstrable lesions, diabetes of a moderately severe grade appears, may persist for a long period, and be followed by such complications as tuberculosis, gangrene, etc., and may finally lead to a fatal result. Naunyn, however, points out that the acidosis of severe diabetes occurred rarely in his cases of hepatic diabetes.

That pathologic conditions of the central nervous system and perhaps of the sympathetic and larger peripheral nerves may give rise to glycosuria and diabetes is, of course, established. The number of neuropathic conditions in which one or the other of these has been found is now considerable. The one definite condition the effect of which is constant is Claude Bernard's *piqûre*; and as bearing out the physiologic relationship existing between certain unknown structures in the floor of the fourth ventricle and the glycogen-store in the liver, may be cited the instances of lesions (hemorrhages, softening, tumors) in man observed in this situation with which glycosuria has been associated. That cerebral and perhaps spinal disturbances other than those in the region of the fourth ventricle may be associated with or followed by diabetes many clinical cases prove. On the other hand, there is no evidence that would show that it is the direct influence of the central nervous system upon the carbohydrate metabolism that produces hyperglycemia and glycosuria. Indeed, the experiments in which the splanchnic were sectioned after *piqûre* (Claude Bernard and others) without producing glycosuria show the necessity of the

interaction of other organs. Similar results follow enervation of the liver and pancreas, while enervation of either organ alone after *piqûre* is followed by hyperglycemia of less grade. Again, in animals already rendered diabetic through extirpation of the pancreas, *piqûre* causes augmentation of the glycosuria.

What the relationship between the central nervous system and the organs of carbohydrate metabolism is we are not informed. Naunyn has proposed a theoretic conception, supposed to render more intelligible this interaction, which is about as follows: "I hold it as proven that diseases of the nervous system lead to diabetes, in that there occurs coincidently disturbances of function in other organs which preside directly over the carbohydrate metabolism; that these disturbances are not simple expressions of abnormal functional activity of the central organs, but using the analogy of the motor in contradistinction to the nutritive or secretory neuron, we can imagine that each stands for an entity, the one acting upon muscle cells (motor neuron) and the other upon secretory cells, as in the liver and pancreas (secretory or nutritive neuron). And just as diseases of the motor neuron in any part set up pathologic changes in the entire system, so may the secretory or nutritive organic cells be influenced injuriously in such way as to give rise to diabetes, because of their connections with diseased nervous structures with which they are indissolubly united and under whose domination they are."

The existence of a renal form of diabetes is still unproven. That the kidneys are not merely passively engaged in the elimination of the urinary constituents is shown by experimental phloridzin diabetes, in which the capacity of the renal epithelium to prevent the excretion of the normal sugar of the blood is diminished and the anomaly of glycosuria without hyperglycemia is observed. That, moreover, the resistance of the renal epithelium varies with different animals has also been shown; in birds, hyperglycemia, after extirpation of the pancreas, is not followed by glycosuria; and in rabbits, chemicals which attack directly and injure the renal cells (diuretin, theobromin) give rise to glycosuria (Jacoby). The appearance of glycosuria in chronic Bright's disease, after renal hemorrhages, etc., has been regarded as speaking for a diabetes of renal origin (Klemperer). The evidence is, how-

ever, inconclusive. On the one hand, albuminuria and diabetes are known not rarely to coexist; while in the case of hemorrhage, calculi are the commonest causes, and the cases might, therefore, be considered as being related to gout (Naunyn). Secondary changes in the kidney, the results of storing of the glycogen in the tubular epithelium, degenerations, etc., are not uncommon. They do not, however, point to the kidneys as early or important factors in the pathology of diabetes.

In the preceding pages I have endeavored to give a sketch of some aspects of the pathology of diabetes. The sketch is necessarily incomplete, and the incompleteness is due only in part to our imperfect knowledge of the subject, for in order to bring the paper within the allotted limits not a few important topics were omitted. Enough has, however, been presented to show that the symptom-complex of diabetes is dependent upon no one primary set of functional and anatomic conditions. Glycosuria, moreover, extends over a wider range than does diabetes, and follows so many and various insults to the body that its significance is minimal. Its appearance may be rapid in the extreme, and its disappearance as sudden. As bearing on the first statement, I might say that in some experiments upon the pancreas in dogs which have been carried out recently by Dr. Pearce and myself, glucose has been demonstrable in the urine within thirty minutes after injections of gastric juice into the duct of Wirsung. Yet such sudden glycosurias have, in not a few instances, especially after injury to the central nervous system, either persisted with the production of diabetes, or, after an interval of absence, been followed by that condition. The organs which would appear to be established as presiding directly over the carbohydrate metabolism are the pancreas and liver. But what the mechanism of the control exercised by them is has not been solved. That nervous influence is essential is proven both by experiment and observation of pathologic states in man, but that the nervous control is specific and other than the ordinary trophic influence is highly improbable. In other words, the carbohydrate control resides in certain somatic cells contained in the pancreas and liver, chiefly in the former organ, and perhaps in still other organs; the integrity of these cells insures physiologic metabolism; pathologic conditions, perhaps func-



tional only, but certainly organic, and not always demonstrable by our present means of study, disturb the control, whence arise, according to the circumstance of duration, severity, etc., transient glycosuria or persistent diabetes. *January 24, 1901.*

### The Urine in Diabetes.

JOHN MARSHALL, M.D.

(BY INVITATION.)

To characterize a urine as being diabetic one must be satisfied that the hexose, commonly known as glucose or diabetic sugar, is present. Accompanying glucose there may also be present, especially in severe cases of diabetes mellitus, the so-called pentoses. These latter, however, are usually present only in small quantity and are fairly difficult of detection, and consequently it rarely occurs that the practitioner finds need to apply tests for their detection. There may also be present, accompanying glucose in severe cases of diabetes, acetone, which, when present in considerable quantity, may be roughly detected by the fruit-like odor which is given off when the urine is heated. Aceto-acetic acid (diacetic acid) and beta-oxybutyric acid very often accompany acetone in the urine. The beta-oxybutyric acid, according to recent researches, is produced by an oxidation process in the body and may be considered as the mother substance of aceto-acetic acid, which latter breaks up into acetone and carbonic acid, and therefore it is that in diabetic urine one is likely to find acetone, which may be considered as the final product of the breaking up of the mother compounds just stated. As glucose is the constituent which occurs in largest quantity in diabetic urine and is the constituent most easily detected, it is the constituent which is the most sought for by the application of tests. While it is claimed that, even under normal physiologic conditions and on a mixed diet, the urine of an individual may contain traces of glucose, even to the extent of 0.02 per cent., this quantity is insufficient to respond to the most delicate tests for glucose when the latter are applied directly, as in ordinary practice, to urine. It is only by complicated methods

of removal of substances from a large volume of urine that the quantity above stated of a cupric oxid reducing substance, calculated as glucose, has been isolated. It might be stated that all chemists are not satisfied that the reducing substance which is contained in the final residue from the urine is glucose.

Since the announcement in 1883 of the phenyl-hydrazin hydrochlorid test, no qualitative tests have been proposed that may be considered as of greater value than those existing before the time stated. The qualitative tests which may be considered as of practical value are limited in number. We may consider the test by means of Fehling's solution, Boettger's test (or Nylander's modification of Boettger's test), the phenyl-hydrazin hydrochlorid test, the fermentation test, and the polarizing-saccharimeter test as being probably the most delicate tests for glucose in urine.

In making the test by Fehling's solution one must be positive that the Fehling's solution has not undergone decomposition. This may readily be determined by diluting the quantity of Fehling's solution to be employed (which is usually about 1 cubic centimeter) with at least four volumes of water, and then heating the diluted liquid to the boiling-point and holding the test-tube containing the liquid in various positions with reference to light, so as to observe whether reduction, as indicated by the presence of a reddish-brown precipitate, usually suspended in the liquid, has occurred. It is obvious that a Fehling's solution that shows the presence of a reddish-brown cuprous oxid after the application of the control test just mentioned should not be employed.

If albumin should be contained in the urine it must be removed before applying Fehling's test. This may be accomplished by the addition of a few drops of acetic acid and boiling the urine so as to coagulate the albumin, filtering, and employing the filtrate for the test.

In applying the test for glucose the diluted Fehling's solution should be heated to the boiling-point and the suspected urine added drop by drop, and the liquid heated to the boiling-point after each addition of the urine, but the boiling should not be continued after, in each case, it has been brought to the boiling-point. If glucose be present reduction of the cupric oxid would

occur with the separation of insoluble, reddish-brown, cuprous oxid, or yellowish cuprous hydroxid. The latter yellowish compound is usually produced when the urine added to the diluted Fehling's solution contains a very considerable quantity of glucose, whereas the reddish-brown cuprous oxid is usually produced when the glucose present in the quantity of urine added is not very great. It not infrequently occurs that, under the above circumstances, an insoluble precipitate is produced in urine free from glucose, which is somewhat similar in color to the reddish-brown cuprous oxid produced when glucose is present in the urine. The precipitate consists of the phosphates of the alkaline earths tinted with coloring matter, produced most likely by the action of the sodium hydroxid of Fehling's solution upon the normal coloring matters of the urine. One may readily distinguish between the cuprous oxid precipitate and the precipitate of the phosphates of the alkaline earths by observing that the cuprous oxid precipitate is distributed homogeneously throughout the liquid, and when it collects as a sediment at the bottom of the test-tube it forms a compact layer, whereas the precipitates of the phosphates of the alkaline earths is flocculent in character and is not homogeneously distributed throughout the liquid, and when it collects at the bottom of the tube as a sediment it does not form a compact layer, but forms a loose layer quite easily disturbed by the slightest agitation of the liquid in the tube.

It should be borne in mind that substances normally present in urine, such as uric acid, creatinin, urine and biliary coloring matters, and compounds of glycuronic acid, may, on the one hand, reduce the cupric oxid of Fehling's solution, and on the other hand dissolve cuprous oxid which may have resulted from the reduction of cupric oxid by a small quantity of glucose. This interference is especially produced when a rather large quantity of creatinin is present in the urine, causing the destruction of the blue coloration of the Fehling's solution and imparting an olive-green color to the liquid without the production of a precipitate. Homogentisic acid, which is present in the so-called alkapton urine, has the property of reducing the cupric oxid of Fehling's solution to cuprous oxid. This substance, which results from the breaking down of tyrosin, is not a frequent constituent of urine.

It may readily be detected by rendering the urine alkaline with sodium hydroxid and agitating the liquid, without heating, in the presence of air, whereupon the liquid will become brownish or black in color, depending upon the quantity of the acid present. It should also be borne in mind that, on the administration of certain compounds, such as salicylic acid, chloral hydrate, thallin, salol, benzosol, saccharin, arbutin, benzoid acid, turpentine, glycerin, and chloroform, substances appear in the urine which possess the property of reducing the cupric oxid of Fehling's solution to cuprous oxid.

Boettger's test is a delicate test, especially when applied as Nylander's modification. If albumin should be present in the urine, it must be removed before making the test by boiling and filtering. The filtrate is then employed to make the test. After the addition of solution of sodium hydroxid to about 15 cubic centimeters of the urine and a quantity of bismuth subnitrate about the size of a large mustard-seed, the urine should be boiled not longer than three or four minutes. In the presence of glucose the bismuth subnitrate will be colored brown or black, the intensity of the color depending upon the quantity of glucose present. In Nylander's modification an alkaline solution of bismuth tartrate is employed, and from one-half to one cubic centimeter of the solution, prepared according to the directions of Nylander, is added to about 15 cubic centimeters of the urine, and the liquid is then boiled. In this case, when the urine is boiled, the liquid throughout its entirety will be colored brownish or black in the presence of glucose. Uric acid and creatinin do not interfere with this test, but indican and, as stated above, albuminous urine, will produce black sulphid of bismuth which cannot be differentiated from the black coloration produced by the action of glucose upon bismuth subnitrate.

It should be remembered that on the administration of turpentine, sulphonal, trional, arbutin, salol, senna, rhubarb, and antipyrin, substances appear in the urine which cause a reduction of the bismuth subnitrate, with the production of a brownish or black substance.

The phenyl-hydrazin hydrochlorid test is a delicate test for glucose, but unfortunately, as usually applied, an adequate quan-

tity of phenyl-hydrazin hydrochlorid is not employed in making the test. In making the test at least 50 cubic centimeters of urine should be employed and a quantity about the size of a small chestnut of phenyl-hydrazin hydrochlorid and a quantity about the size of two small chestnuts of sodium acetate should be added, and the beaker containing the liquid should be warmed on a water-bath at the temperature of boiling water for one-half to three-quarters of an hour. The beaker containing the liquid should then be placed in a vessel containing cold water and allowed to stand several hours to permit crystals of phenyl-glukosazon to form. The yellow, needle-like crystals, usually arranged in sheafs, may then be collected on a filter paper, or may be removed directly from the liquid by means of a wide-mouthed pipet, and placed on a glass slide and examined under the microscope. If the insoluble substance which separated should not be crystalline in character, corresponding to the well-known crystal forms of the osazone compound, it may be collected on a filter and dissolved in hot alcohol. The alcoholic solution may then be treated with water and the alcohol evaporated by the application of heat, whereupon the osazone compound should separate in the characteristic crystalline form. These crystals should melt at a temperature of between  $204^{\circ}$  to  $205^{\circ}$  C. It is claimed that glycuronic acid in urine will produce a crystalline compound with phenyl-hydrazin hydrochlorid, but the melting point of this compound is  $150^{\circ}$  C. as against the higher melting point of the other compound.

The fermentation test is of very definite value, provided the urine should contain not less than 0.4 per cent. of glucose. The quantity of carbon dioxid given off in the fermentation of about 0.4 per cent. of glucose is about sufficient to saturate, and therefore remain dissolved in the liquid in which the glucose was contained. Under these conditions it is obvious that there will be no visible appearance of a gas having been produced. In the application of this test a control test with yeast and a urine free from glucose or water alone should be employed, so as to observe whether the yeast itself does not produce gas. The gas produced should also be tested by the introduction of sodium hydroxid into the tube containing it. Absorption of the gas by

the alkaline liquid will indicate at once that it consisted of carbon dioxid.

The test for glucose by means of the polarizing-saccharimeter is of value, provided the instrument is of high grade. The delicacy of the test for glucose by means of this instrument, even though the instrument should be adapted for the detection of the smallest quantity of sugar, is not as delicate as the test with Fehling's solution. The cost of an instrument of the highest grade precludes its coming into general use among practitioners.

In conclusion, it may be said that substances which are sometimes added to urine to prevent its decomposition are capable themselves of reducing cupric oxid in alkaline solution to cuprous oxid. This reducing property is possessed by formaldehyd, chloroform, and chloral hydrate. Ordinary ether and also salicylic acid do not possess this reducing action upon alkaline cupric oxid solutions.

*January 24, 1901.*

#### DISCUSSION.

DR. WADSWORTH: In addition to what has been said there are several very important considerations that should be thought of at this time.

The problem, the speaker said, was a biologic one. The intake and output of carbohydrates and sugar and the measure of the same was of great importance as an indication of the severity of the morbid processes, but by itself gave very little insight into the nature of the disease.

The protoplasm in diabetes produced abnormal sugar under certain disturbing influences, and what these were could be determined by a study of the beginning and progress of the disease as it appeared clinically. The systematic study of a large number of cases was of great importance. There was a group of clinicians in England who paid special attention to this disease who were skilled laboratory men, and whose experience and conclusions were not to be lightly set aside. They found that diabetes was a disease apart from the kidneys—frequently that it was very generally associated with functional disturbance of the nervous system (the glycosuria following the nervous disturbance). That treatment directed to the building up of the protoplasmic tone of

the system, especially with reference to the nervous system, was of far more value than an attempt to treat the glycosuria directly through the supply of hydrocarbons; that diet apart from the hydrocarbons played a very important part of the treatment. They cited cases where glycosuria followed nervous shock. They further showed that if the nervous conditions recurred or were continuous the diabetic conditions varied with the nervous conditions and truly depended on them *post hoc* and *propter hoc*.

Clinicians could not, without being quite absurd, ignore the valuable work and conclusions of these men simply because they had learned a few facts, some of them not being relevant to the problems of the disease. The knowledge of the significance of the pancreas was in perfect harmony with their observations. It was known that the pancreas was very sensitive to nervous impulses, both as to its excretion and circulation. He had personally examined several hundred postmortems, and had repeatedly found them congested where there was irritation of stomach and duodenum. It was known that they acted by a reflex mechanism, which, it must be believed, was subject to influence from the general nervous system. If it was found that the protoplasm that produced the pathologic sugar was located in the pancreas, clinicians would still have to return to the question of why it did so under certain conditions, and this question would still be the main question after it had been determined how much of internal secretion, how much of tissue degeneration, and how much of functional disturbances was associated with the symptoms.

DR. RIESMAN wished to compliment Dr. Edsall upon his masterly presentation of a most difficult subject—a presentation which was not only clear, but authoritative, and showed an excellent knowledge of the literature. He had made autopsies on two cases of diabetes, and had found in both arteriosclerosis. One of the cases was a girl of thirteen, whose arteries and heart valves showed distinct sclerotic patches; the other was an adult in whom the arteriosclerosis was not surprising. There were apparently two types of cases: in the young the arteriosclerosis was probably a consequence of the diabetes; in the other form, the mild diabetes seen in advanced life in gouty subjects, the arteriosclerosis seemed to precede the diabetes. Whether it acted as a contributory cause

the speaker was unable to say. Clinically, the latter group of cases ran a much milder and more prolonged course than the former. Regarding the hyperglycemia, he wished to ask Dr. Edsall whether it could not exist without a marked or corresponding glycosuria. It seemed to him that in cases in which renal disease developed with the coincident diminution of sugar in the urine there might be a hyperglycemia of which the glycosuria was then not a correct index. Regarding Bremer's test, he had been disappointed in it. In a number of tests made with methylene-blue he had failed to secure the difference in color between diabetic and normal blood. With reference to the phenyl-hydrazin test, to which Dr. Marshall had alluded, he would say that he had used a modification recently advocated which greatly simplified the test, so that it could easily be done in ten minutes, and without the use of the water-bath. Typical crystals had regularly been obtained in his clinic by this modification in a very few minutes.

He had used methylene-blue to some extent in the treatment of diabetes. As in other conditions when methylene-blue was given the urine turned blue immediately in every case but one, and in that patient, although three grains a day were given for weeks, the urine never turned blue. The same pills were given to other persons and produced a blue coloration of the urine. It was not possible to develop the blue color in the urine of the patient either by reduction or oxidation, or by the addition of alkalies or acids, and he was entirely unable to explain the phenomenon. Regarding the theory of diabetes, Dr. Edsall had not directly referred to the theory of the internal secretion advocated by Lépine, who held that there was normally a glycolytic ferment furnished by the pancreas which destroyed any excess of sugar that might accumulate in the blood. It was the absence of this ferment that gave rise to diabetes. The hypothesis had even been advanced that diabetes was an infectious disease. It was needless to say that no proof whatever of the last view had been brought.

DR. MCFARLAND said that Cohnheim was the first to propound the ferment theory of diabetes as early as 1877. The nervous theory had even been used to explain pancreatic diabetes, it being maintained that important sympathetic nerves were injured in the extirpation of the pancreas; but the fact that the subcutaneous



implantation of a small piece of the pancreas prevented diabetes, until its subsequent excision, disproved this view. He had made an autopsy on one case of diabetes and found no microscopic lesions. Regarding arteriosclerosis, he had recently met with it in two young persons in whom diabetes had not existed.

DR. COPLIN said that he had made autopsies on four cases of diabetes. He was pleased to find that Dr. Flexner could identify the liver as from a diabetic by the presence of glycogen. In his (Dr. Coplin's) experience glycogen had disappeared very early and was hard to demonstrate. He had examined the bodies of Langerhans with great care in one case, and had found only a few sclerotic areas at the margins. Sometimes the head of the pancreas was enlarged, even resembling cancer. This was due to an interstitial pancreatitis. Dr. Harris had found changes in the salivary glands. A blood change to which he wished to refer was the glycogenic reaction of the leukocytes. His experience with Bremer's test was at variance with that of Dr. Riesman. He believed that failures were due to the unreliability of anilin dyes, particularly methylene-blue. He was under the impression that hyperglycemia, as had also been maintained by Barlow, was by no means the invariable rule in diabetes.

DR. HARTZELL said that there were certain lesions of the skin in diabetes, interesting clinically, diagnostically, and pathologically. The processes varied, some were inflammatory, some of the nature of new growths, some brought about a death of the skin and subcutaneous tissues. Some of the lesions were due to micro-organisms, and even the mere presence of sugar was sufficient to influence the skin unfavorably. Diabetic gangrene, when affecting the extremities, might be due to arteriosclerosis, but the latter could not explain those cases following slight injuries. In them the gangrene might be due to bacteria or to the sugar itself. The latter view was adopted by Unna, who held that the sugar might act as a reducing agent. The so-called xanthoma diabeticorum was not satisfactorily explained. The peculiarity of the skin lesions in diabetes was that they could be studied from beginning to end during the patient's life.

DR. WILLSON stated that he believed the best test to be that with phenyl-hydrazin hydrochlorid, which, as Dr. Riesman had

said, could be carried through in about ten minutes. Given briefly, the test was to take at least half a test-tubeful of urine, to add two parts of sodium acetate (about as much as half a lima-bean), and half as much phenyl-hydrazin hydrochlorid. This was allowed to boil and then cooled slowly. He had modified this test in the following way: Instead of allowing the solution to cool in the test-tube, he had put a drop on a slide and allowed it to cool there. Crystals formed in from one to three minutes. The test was also rendered delicate and certain by using equal parts of sodium acetate and phenyl-hydrazin hydrochlorid. Only the day before he had had occasion to demonstrate the reliability and delicacy of the test. In urine from a patient who was diabetic, in which he had first failed to get a reaction with Fehling's solution, he obtained by the above method typical crystals with phenyl-hydrazin. After cooling the Fehling test also showed a suspicious, but never complete reaction. Ordinarily, the crystals could be seen with the low power of the microscope, but in very low percentages of sugar search should be made for them with the highest power lenses, since the crystals were often correspondingly minute. One fallacy of no great importance was that levulose as well as glycuron acid also gave the phenyl-hydrazin reaction. The former occurred rarely except in the presence of glucose. The latter could easily be excluded by its failure to react with Nylander's bismuth solution and with the fermentation test.

DR. SHUMWAY spoke of the peculiar change in the pigment layer of the iris in cases of diabetes, consisting in an enormous swelling and edema of the pigment cells on its posterior surface. He suggested that those in a condition to obtain eyes from diabetics at autopsy should preserve them for a careful study. It might be best to put them in absolute alcohol.

DR. EDSALL, concluding the discussion on diabetes, emphasized the importance of remembering that after chloroform anesthesia the urine would reduce Fehling's solution, a fact which accounted for many of the reports of what had been considered to be glycosuria after operation in which chloroform was used. Dr. Edsall had observed this point in dogs in experimental production of diabetes, and noted that it was likely to lead to confusion in such work. The relation of digestive disturbances to diabetes had been men-

tioned by others, but such disturbances had no serious relation to diabetes, and it was worthy of note that in the course of the disease they were likely to decrease the glycosuria rather than to increase it, because they reduced the absorption of food. In reply to Dr. Riesman, he stated that hyperglycemia is likely to disappear in renal disturbance, when the latter is a terminal affection, because the amount of food taken is usually very considerably reduced. There did seem, however, to be in some cases of marked renal disturbance some degree of hyperglycemia without corresponding glycosuria, though as a rule the glycosuria was a fair index of the degree of hyperglycemia as well as of its presence. As to the influence upon methylene-blue observed by Dr. Riesman, he suggested that it was possible that alterations in the blood alkalinity had caused the variations in excretion. The decolorization of methylene-blue by diabetic blood seemed to depend upon two factors, the presence of sugar and the existence of a considerable degree of alkalinity of the test fluid. It is possible that diabetics who were suffering from a considerable degree of acid intoxication could not decolorize methylene-blue in their own body fluids, owing to the reduction of the alkalinity of the blood, while a diabetic who had a considerable degree of hyperglycemia, but yet had a normal degree of blood alkalinity, would decolorize the methylene-blue.

In reply to Dr. Coplin, he stated that contrary to earlier results the work done by modern methods showed a hyperglycemia in diabetes with practically no well-established exceptions. Experimental phloridzin diabetes could be used in this argument; in this variety of glycosuria there was no hyperglycemia, but the condition was not at all comparable to the disease as it occurred in man. The relation of the salivary glands to diabetes was probably a very unimportant one. Such a relation had never been satisfactorily shown by experiments, though some work, particularly that of Minkowski, had indicated that these glands might have an unimportant relation to the disease. The work of the author mentioned, however, had shown that these glands could not substitute in the performance of the function of the pancreas.

### Fatal Polypoid Colitis Resulting from Administration of Inunctions.

WILLIAM EGBERT ROBERTSON, M.D.

Colitis may occur alone, or may exist as a part of a general inflammation of the bowel. The causes of intestinal inflammation are many, though they may be categorized under two headings, viz.: those due directly to some change in the bowel contents and those resulting from the introduction of poisons—animal, vegetable, or metallic—or to the introduction of microorganisms capable of bringing about decomposition. Irrespective of the factor concerned in their production, the lesions are the same, varying from a simple catarrhal process to the most extensive diphtheritic and destructive one. In the milder forms there is more or less injection and swelling of the mucosa, and if the condition persists for some time, productive inflammation of the connective tissue elements ensues. In the severest cases, the diphtheritic and destructive ones, there is an intense desquamation, often an exfoliation of portions of mucosa, with exudation, extravasation of blood, fibrin formation, the whole entangling detritus and fecal portions constituting a pseudomembrane. Ulceration occurs in some cases secondarily to the diphtheritic process, in others as a result of sloughing of an ischemic area induced by thrombosis.

A certain amount of desquamation occurs in all forms, and usually more or less regeneration, except in the most acute and intense cases; but this latter function is lost in time, and in consequence atrophy results. According to Nothnagel, atrophy of the mucosa of the large intestine, especially that of the cecum, may be considered more or less normal to late adult life, as it occurs in about 80 per cent. of all such subjects coming to autopsy. This is probably due in part to pressure and in part to regressive changes in the lymphoid elements incident to old age.

The more severe and chronic forms of intestinal inflammation are prone to occur in the large bowel, as the so-called apostematic form, with sinuous erosions, and often more or less well-developed polypi, and with islets of tissue bridging between the ulcerated areas. Such a case was the one which I wish to present, the

patient having been under the care of Drs. Stewart and Moore at the Episcopal Hospital.

J. H., male, aged forty-four years, was never very robust. Beginning sometime in 1896, for two years and ten months he was employed as an attendant upon a locomotor ataxic patient, during which time he administered the inunction cure. Salivation and diarrhea developed very promptly, and the latter has been constant since—from four to twenty movements daily. Stools always are thin, containing more or less mucus, usually some blood, and at times clots. There was considerable flatulence and occasionally vomiting. He had abdominal pain, especially in the left iliac region, for about three months preceding his demise. His general condition progressively deteriorated. He lost flesh, became cachectic, breath became very foul, the mouth and teeth were in very bad condition, with suppurating gums, from which Dr. Ghiskey obtained a streptococcus. He had facial erysipelas for several days prior to the fatal issue, which was due to peritonitis.

*Necropsy.* Body of a poorly nourished man. Very little subcutaneous fat; musculature poor; rigor mortis very pronounced.

*Thoracic Cavity.* Lungs very emphysematous; slight hypostatic congestion; no scars in apices; no pleural adhesions.

*Heart.* No valvular lesions; some atheroma of the aorta; pericardial fluid slightly increased in amount.

*Abdominal Cavity.* On opening the abdomen the ascending colon presented, the cecum being much dilated and displaced two-thirds of the way over to the left side, and ascending (as the colon) to the normal position of the hepatic flexure. The appendix was sharply bent on itself, slightly injected toward the free end, no abnormal attachments. Several coils of the small intestine were adherent deep down in the true pelvis, a little turbid fluid bathing their most dependent portion. The peritoneum over the right pelvic wall was injected. A little pus about the right brim. Left pelvic wall was not visible, being covered by the rectum and sigmoid above, these firmly adherent, and part of the contents of a large pocket formed by the great omentum above, the abdominal parietes and pelvis to the outer side, great omentum and small intestine internally. On stripping the omentum up, fecal contents

and turbid peritoneal fluid were found in the pocket. Several perforations existed in the descending colon and sigmoid flexure, and the bowel wall was greatly softened and in places almost pultaceous.

On removing the colon in its entirety it was found to be the seat of a high-grade ulcerative condition, between which were islets of more or less hypertrophic mucosa and polypi, extending from the ileocecal valve to the lowest part of the rectum. The lower third of the rectum was greatly thickened, this having led to the diagnosis of rectal carcinoma during life, its mucosa and submucosa being the seat of a moderate mucoid change and considerable deep ulceration. The small intestine presented no abnormality. The stomach was chronically inflamed and much thickened. Spleen slightly enlarged and softened; liver enlarged; no gallstones in duct or bladder; the kidneys were the seat of both parenchymatous and interstitial change; no chalky deposits were perceptible to the naked eye.

Cultures from the peritoneal fluid were examined by Dr. Ghriskey, and found to contain the bacillus pyocyaneus, colon bacillus, and streptococcus. Microscopically, sections from the ulcerated areas showed more or less complete destruction of the mucosa and submucosa, and in several places all of the coats of the bowel. The hypertrophic areas were made up in part of proliferated mucosa, but more largely by an increase in the connective tissue elements. Absolutely no suspicion of malignancy was found in the rectal thickening.

Sections from the kidney presented diffuse cloudy swelling of the epithelial elements, with small foci of necrosis, increased amount of interstitial tissue with thickening of the bloodvessel walls. No lime infarcts or deposits were found. Salkowsky<sup>1</sup> was the first to call attention to the deposition of lime salts in and about necrotic cells of the straight tubules of rabbits poisoned by corrosive sublimate. In man the condition is less constant in mercurial poisoning, and, when present, is apt to occur about the cells of the convoluted tubules. It may also be deposited in hyalin casts within the urinary tubules. Though such a condition is spoken of as "sublimatniere," it is not constant, nor is it pathognomonic of mercurial poisoning, for it is sometimes seen in poisoning by bismuth, potassium chromate, phosphorus, and in disturbed circu-

lation, the calcification in each case involving necrotic epithelial cells. The parenchymatous changes in the kidneys of the case under consideration were not due to mercury, but occurred as a terminal infection, in all probability more or less intimately dependent upon the intestinal trouble. The inference seems justifiable that the bowel lesion in this case was originally induced by the mercury. It is well known that a single large dose of the drug in any form is less apt to produce ill effects than even a smaller amount given in divided doses. Mayençon and Bergeret<sup>2</sup> gave 1 cg. of corrosive sublimate hypodermically to a dog. The urine contained mercury for the next twenty-four hours, afterward none was found. When 1 cg. was given daily for ten or twelve days, mercury could be recovered for four or five days after the administration of the drug had ceased, thus seeming to indicate that in repeated doses elimination ceases before the body is entirely free. The chief avenue of escape is the kidneys, but it is also eliminated by the salivary glands, pancreas, and intestines. It has been found in the blood, urine, feces, saliva, serum of ulcers, seminal fluid, pus, in milk of nursing women; in fact, in every tissue of the body, also in aborted fetuses of salivated women, and in the urine of a baby whose wet-nurse was taking calomel. Schuster<sup>3</sup> found it in the feces three months after a mercurial course, and he believes it takes about six months to rid the system after mercurial medication. Kussmaul and Gorup-Besanez<sup>4</sup> were able to recover it from the liver twelve months after administration. Ludwig<sup>5</sup> claims to have found it in the tissues of a syphilitic many years after the cessation of treatment. The symptoms and ultimate issue depend on the dose and mode of absorption. Kaufmann<sup>6</sup> speaks of a case of a man, aged thirty years, who took on an empty stomach eight to ten grs. of corrosive sublimate in normal salt solution. He continued to drink salt solution. Death occurred after two hours of violent pain and vomiting. This case is of particular interest for two reasons: first, because of the extraordinary promptness with which death supervened, and secondly, the esophagus, stomach, and small intestine were the seat of a diphtheritic necrosis, the result of direct action of the poison, though this was doubtless facilitated by the frequent draughts of salt solution.

As a rule, however, the large intestine is involved in mercury poisoning. In acute cases the most intense diphtheritic inflammation results, while ulcerative lesions predominate in the chronic forms. In either case, Kaufmann<sup>7</sup> does not believe the lesion to result from erosion due to the elimination of mercury, but rather to blood stasis and thrombosis. Circulatory disturbances render the mucous membrane of the bowel unable to withstand the action of the various microorganisms, and diphtheritic necrosis or ulceration results. The most intense necrosis may occur when the dose of mercury has really been too small to act as a direct irritant; and, on the other hand, very large doses may be ingested without the participation of the bowel. Yet Kaufmann's case, referred to above, proves that direct local action may occur.

Artisans or others exposed to the vapor or continuous administration of some form of the drug acquire a condition somewhat resembling paralysis agitans; or, on the other hand, a mercurial cachexia which closely mimics scurvy, characterized by anemia, emaciation, loss of power, loss of hair, pains and aches in bones and joints, fetid breath, swollen gums, diarrhea, and generally disordered secretions. Such was the picture presented by the case just reported.

Children born of parents who are the subjects of chronic mercurial poisoning are usually feeble, often rickety, and specially prone to develop tuberculosis.

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### Sarcoma of the Small Intestine in a Child of Five Years.

WILLIAM EGBERT ROBERTSON, M.D.,

AND

ELLIS E. W. GIVEN, M.D.

Sarcoma of the small intestine, being of such rare occurrence as to render of interest each case reported, leads us to place upon record the clinical history and postmortem findings in a child



recently in the Episcopal Hospital under the care of Drs. Henry M. Fisher and Richard H. Harte, to whom we are indebted for the privilege of presenting the specimen this evening.

Until Libman published his five cases in the September issue of the *American Journal of the Medical Sciences* for 1900, very little had been written upon the subject. It is hardly mentioned in many of the text-books, and where so mentioned they all agree in regarding primary sarcoma of the small intestine as a very rare condition.

Birch-Hirschfeld says Madelung published in 1892 three cases observed by himself, and was able to collect but eleven other cases from the literature; that they are met with between the thirtieth and fortieth years of life, but they are not infrequently met with in children.

Stern has described a case of congenital, small round-celled sarcoma, with hyaline degeneration of the vessels. In this case the tumor caused complete obstruction of the bowel, which is quite an uncommon condition.

Ziegler merely says that connective tissue tumors are rare and have far less significance than cancer.

Kaufman says "the growths are usually diffuse and are met with especially in children; they are round or spindle celled, originate in the submucosa, and soon spread to the muscularis and mucosa, and, as a rule, do not attack the serosa. Stenosis is the exception, since the involved bowel is generally paralyzed. In consequence of this, dilatation is frequent and aneurysm-like dilatations are common."

Bessal-Hagen reports the case of a seven-year old boy in whom, during the course of an extensive sarcomatous infiltration of a portion of the jejunum, there had been formed an enormous aneurysm-like dilatation of the size of a large man's fist.

Ribbert fails entirely to even mention the condition.

Ewald, quoting Fleisher, states that but "fourteen cases are recorded in literature up to the present time" (1897).

Stengel says that "sarcoma of the intestine is rare. Round-celled sarcoma, springing from the submucosa and deeper layers of the mucosa and sometimes infiltrating the mesentery, may also occur as an independent and primary affection."

Eshner simply states that such tumors are rare, but that when they do occur they attack males a little more frequently than females, and occur rather earlier in life than malignant disease elsewhere.

The patient from whom the specimen presented this evening was removed was a boy, five years of age, of Italian parents, admitted to the hospital October 5, 1899, with a very indefinite history as to his previous condition, all that was obtainable being that he had been sick for about one month past, suffering with painful periodic distention of his abdomen, which would continue for a few days, and then disappear. Between the attacks the child was apparently in perfect health.

When admitted he was only a fairly well-developed child. Slightly coated tongue, no jaundice. Heart and lungs clear. The abdomen was much distended and tympanitic and so painful and tender as to render an examination quite unsatisfactory, the tenderness being more pronounced in the right iliac fossa, and at first leading to a tentative diagnosis of appendicitis. Spleen enlarged. After the bowels were thoroughly opened the abdominal pain and tenderness, with tympany, largely disappeared and permitted a more satisfactory examination of the abdomen. In the median line, about half-way from the symphysis pubis to the umbilicus, could be felt a hard, non-painful and seemingly nodular mass about the size of a lemon, which was slightly movable and quite dull on percussion.

An examination of the blood at this time by Dr. Ghiskey showed a leukocytosis of 21,300, a differential count showing: polymorphonuclear leukocytes, 66.6 per cent.; small lymphocytes, 24 per cent.; large lymphocytes, 9.2 per cent.; eosinophiles, 0.2 per cent.

The urine had a specific gravity of 1017, was faintly acid, cloudy with phosphates; albumin was not present, and peptone and albumoses were absent. His weight at this time, one week after admission, was thirty-four pounds.

The diagnosis being comparatively clear and the child failing rapidly, an exploratory operation was decided upon and performed November 1st, just twenty-five days after the child came under observation and, according to the history obtained from the parents, two months from the earliest indication of trouble.

Under ether the abdomen was opened in the median line, and about 75 to 100 c.c. of brownish fluid escaped. A large, irregularly hard, nodular mass was found so intimately associated with the small intestine as to entirely preclude all attempts to remove it, and the abdomen was closed, leaving a gauze drain in place. The child was under ether about twenty-five minutes.

Following the operation the growth rapidly increased in size, and a fecal fistula developed at the site of the gauze drain. The patient rapidly lost weight and strength, and died November 24th.

The anemia, emaciation, and constitutional depression, as noted by authors already referred to, were extreme, and developed rapidly in this case, and were due in large part to the high location of the tumor, involving, as it did, the jejunum, the food after leaving the stomach passing out of the intestine through the fistula.

*Postmortem.* Body of a much emaciated male child. Rigor mortis pronounced in the lower but not in the upper extremities. Drainage protruding from an operation wound in the median line of the anterior abdominal wall about on a level with the umbilicus. On opening the abdomen through the operation wound in the median line the tissues of the anterior abdominal wall parietes are found adherent to an underlying mass for about one and a half inches surrounding the wound. The mass, which is about 15 cm. in diameter, is hard, nodular, and irregularly circular in shape, with a central opening appearing to communicate directly with a large cavity posterior, occupies the median line and extends to the left and above; it is partly covered with great omentum and transverse colon, both of which can be reflected upward; the transverse colon is adherent to the tumor. Coils of small intestine are matted together and pushed upward and to the right, occupying a small space just below the liver. Peritonitis is present throughout the abdominal cavity, particularly posterior and to the side of the mass.

After removing the viscera from the body it was found that the tumor was hollow, the walls of which were  $1\frac{1}{2}$  cm. in thickness. There was an opening about 3 cm. in diameter in the anterior surface, which during life had communicated with the operation wound and had given origin to the fecal fistula.

The sarcoma originated in the submucosa of the upper portion of the jejunum, and extended until it had surrounded the jejunum,

the lumen of the intestine corresponding to the cavity of the tumor. The jejunum entered the mass at the left-hand lower corner, and left it at the right-hand upper corner. The cavity of the tumor measured about 10 cm. by 6 cm. The mass was adherent to the rectum, sigmoid, and bladder. All the organs were practically normal. No metastases were found anywhere in the body.

June 13, 1901.

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- I. Tuberculosis of the Larynx, with Cancer of the Esophagus.  
 II. Cancer of the Esophagus, with Perforation of the  
 Trachea. III. Diffuse (Congenital?) Dilatation  
 of the Esophagus. IV. Tuberculosis and  
 Abscess of the Larynx, with Perfora-  
 tion of the Esophagus.

RICHARD MILLS PEARCE, M.D.

I. (*Service of D. Tyson, Philadelphia Hospital.*)—*Clinical Notes.* Male, aged sixty-four years, ill for three months, and under treatment for pulmonary tuberculosis. No laryngeal symptoms were present except cough. For two months there had been very difficult deglutition, the patient taking very little solid food, and subsisting almost entirely on liquid diet.

The description of the appearance of the larynx and esophagus as seen at the postmortem examination follows:

*Larynx.* Irregular diffuse swelling, extending from tip of epiglottis to below vocal cords. Surface granular, with superficial loss of substance over tip of epiglottis and over vocal cords. On section, mucosa and submucosa pale and glistening, varying slightly in thickness. The new tissue shows no great tendency to invade the structures below the submucosa.

*Histologic examination* confirmed the provisional diagnosis of tuberculosis.

*Esophagus.* Six cm. above the pylorus, in the posterior wall, is a dense, firm mass 1.6 cm. in diameter and 4 mm. thick. The surface shows a loss of the superficial epithelium, and is injected and granular. On section the newly-formed tissue is seen to be dense, grayish-white, and almost fibrous in consistence. Corresponding to the mass is a moderate constriction of the lumen of the esophagus.

*Histologic examination* shows a very early squamous-celled carcinoma.

Other lesions in this case were chronic pulmonary tuberculosis, tuberculous ulcers of intestine, chronic diffuse nephritis, chronic obliterative pericarditis, and arteriosclerosis.

II. (*Service of Dr. Ashton, Philadelphia Hospital.*)—*Clinical Notes.* Male, aged seventy-four years, ill for three months. The early symptoms were sore-throat and cough, with mucopurulent expectoration; difficult deglutition, which became rapidly worse until even liquid diet became impossible; gradual loss of power of speech, which became complete two days before death.

Examination of throat by Dr. Gleason showed injection of posterior roof of pharynx, atrophy of tonsils, cadaveric posterior of left vocal cord. The clinical diagnosis was pulmonary tuberculosis, possibly tuberculosis of larynx, and some mediastinal lesion, causing pressure on left recurrent laryngeal nerve.

At the postmortem examination the following condition of the esophagus was found: Beginning at lower margin of pharynx and extending 8 cm. along esophagus is an irregular fungoid growth, involving the entire circumference of the esophagus, which is greatly dilated. Surface is ulcerated, grayish-red, nodular, and necrotic, with foul odor. On section, growth is gray, opaque, firm, and finely granular. Posteriorly it has extended through wall of esophagus and invaded the prevertebral tissues. Three and a half cm. from upper border of ulceration there is a communication with the trachea, corresponding to the eighth and ninth tracheal rings. The circumference of this perforation is 1.2 cm. On tracheal side the edges of perforation are very irregular, elevated, indurated, and grayish-red, with nodular infiltration of the surround-

ing submucosa. Except for injection, the trachea and larynx are normal.

The following conditions were also present: Chronic bronchitis, emphysema, edema and congestion of lungs, acute splenitis, arteriosclerosis, chronic mitral endocarditis, hypertrophy of heart, general chronic passive congestion, chronic diffuse nephritis.

III. (*Service of Dr. Hughes, Philadelphia Hospital.*)—*Clinical Notes.* Negro, aged fifty-two years. For years patient had a feeling of discomfort at a point just below and to the left of sternocostal angle. This discomfort was greater after eating. The patient was under observation for five weeks. During this time he became greatly emaciated; occasionally vomited a large amount of dark fluid containing black clots, and toward the end of illness small quantities of dark fluid and clotted blood. Physical examination elicited tenderness in epigastric region. No pain at any time. No mass palpable. Muscles of epigastric and right hyperchondriac region rigid on palpation.

A rapidly increasing huskiness of the voice led to an examination of the throat by Dr. Gleason, who found a chronic inflammation of the mucous membrane and paralysis of the vocal cords.

At the autopsy the esophagus was found to be dilated throughout its entire extent. *Measurements:* Thirty-one cm. from pharynx to cardiac orifice; greatest circumference just above cardiac end, 18.3 cm.; at cardiac orifice, 4 cm.; circumference at a point 15 cm. below pharynx, 12.5 cm. The mucosa is much thickened, showing irregular, elevated, grayish, finely granular plaques, between which are depressed smooth black areas. The glands about trachea and esophagus are greatly enlarged and contain soft puriform foci. The largest of these glands is 3 × 5 cm. Over these enlarged glands pass the recurrent laryngeal nerves.

In the absence of any evidence of stenosis, compression, or traction, this condition is considered to be primary, possibly congenital. The enlarged glands cannot be considered as being in any way responsible for the dilatation. Their position was not such as to produce either pressure or traction, and the lesion in them was an acute one. The paralysis of the vocal cords may be explained by the pressure on the recurrent laryngeal nerves, due either to the dilated esophagus or to the enlarged glands.

Upon histologic examination the grayish plaques were found to consist of a greatly thickened epithelium closely resembling that of the skin, while in the depressed areas there was a loss of epithelium, with infiltration of round cells.

In addition the following lesions were present: Chronic diffuse nephritis, chronic splenitis, chronic pleuritis, edema of lungs.

IV. (*Service of Dr. Stengel, University Hospital.*)—*Clinical Notes.* Male, aged twenty-eight years, white; family history negative. Personal history is negative, except for an attack of gripe six years ago.

Symptoms of pulmonary tuberculosis developed in August, 1899. Discharge from left middle ear in June, 1900, which has been continuous since, and has been accompanied by deafness. In September of this year paralysis of the left side of face developed. Since September, 1900, a hoarseness of voice has been present. As the result of examination of the ear, Dr. Milliken made a diagnosis of tuberculosis of middle ear. After examination of the larynx Dr. Grayson reported the condition to be a subacute inflammation, probably tuberculous. Tubercle bacilli were found in the sputum and in the discharge from the middle ear. For two weeks before death the throat was somewhat congested and very painful, and patient vomited occasionally. There were no distinct symptoms pointing to perforation of esophagus. At the autopsy the following condition of the organs of the neck were found:

*Pharynx.* The anterior wall above the orifice of the larynx is irregularly nodular, grayish-red in color, with small areas of ulceration. The nodules are glistening, gray in color, and most numerous and prominent in the upper portion, where the mucosa is also greatly swollen. The ulcerated areas lie between these nodules, and are shallow, narrow, irregular, and grayish-red in color. The posterior wall is not greatly involved, the nodules being smaller and more widely separated.

*Esophagus.* In the anterior wall of the esophagus, at the level of the cricoid cartilage, is an orifice 0.4 cm. in diameter, which is continuous with the cavity of the larynx. The edges of this orifice are injected, greenish-red in color, and fairly smooth. To the left of this opening is a superficial loss of substance 0.2 cm. in

diameter, involving only the mucosa; 1.3 cm. above and to the left of the perforation a spicule of disorganized laryngeal cartilage protrudes through the esophageal mucosa, which at this point is thickened and injected.

*Larynx.* The anterior surface of epiglottis shows numerous small grayish tubercles in and beneath the mucosa. On the posterior surface these are less numerous. The edges of the orifice of the larynx are swollen, irregular, and opaque. This nodular swelling extends down over the vocal cords, which are greatly swollen, and affects the entire mucosa of the larynx and that over the upper three rings of the trachea. Here and there are seen small, superficial losses of substance. Section through the upper portion of posterior wall of larynx, which is 1 cm. in thickness, shows a smooth glistening tissue, in which are small gray or yellowish tubercles. In the posterior wall of the larynx, at a point corresponding to the perforation in the esophagus, is an irregular cavity  $2.1 \times 1$  cm., which connects with the cavity of the larynx. The walls of this cavity are greenish-yellow in color, necrotic, and irregular. It contains a small amount of greenish-yellow pus, with foul odor. The cartilage of the larynx at this point is disorganized, one small fragment lying free in the abscess cavity; another, as mentioned above, perforating the esophagus.

The mucosa of the trachea is injected. Both larynx and trachea contain a considerable amount of thick, greenish-yellow, mucopurulent material. The tracheal lymph nodes are swollen and soft, and contain numerous miliary grayish foci. Thyroid gland, tonsils, and tongue normal.

The anatomic diagnosis of the case includes the following lesions: Tuberculosis of the lungs, with cavity formation; tuberculosis of the intestines, mesenteric lymph nodes, prostate, left seminal vesicle, vas deferens, and epididymis; tuberculosis of left middle ear, with involvement of petrous and mastoid portions of temporal bone, and extension to the dura; fatty degeneration of heart, liver, and kidneys. Histologic examination confirmed the diagnosis of tuberculosis of the larynx. Sections passing through perforation in esophagus show no evidence of tuberculosis. The deeper portions of the tissue, however, are extensively invaded by cocci and a leptothrix

June 13, 1901.



A Case of Trichinosis, with Remarks on (1) Trichinosis, and  
(2) Eosinophilia.

R. C. ROSENBERGER, M.D.

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The clinical history of the patient will be published elsewhere by Dr. J. Chalmers Da Costa, to whom I am indebted for the specimen examined.

*Pathologic Report.* The specimen consists of a small irregular tube of muscular tissue, each side measuring 2 cm.

A small portion was fixed in 1 per cent. osmic acid, dehydrated, and embedded in paraffin; the remainder of the specimen was fixed in Heidenhain's solution, dehydrated, and embedded in paraffin.

Sections were cut and examined in the unstained condition (those fixed in osmic acid); others were stained with hematoxylin and picric acid, hematoxylin and eosin, and with Van Gieson's mixture.

Upon microscopic examination the specimen is seen to be made up of transverse, longitudinal, and oblique sections of striated muscle.

Some fibers show cloudy swelling (the striations are not demonstrable), while others are irregular and wavy. Here and there are small areas in which fragmented, split fibers are seen. The muscle nuclei are, for the most part, normal, but in some areas a notable proliferation is clearly in progress. Small and large recent hemorrhages are seen mostly between bundles of fibers, while one or two extend into and between the individual fibers. Increase in the amount of connective tissue is evident in some areas, and large numbers of small round cells and spindle-shaped cells, with rod and irregular wavy nuclei, are present.

Between, and sometimes in, the muscle fibers encapsulated parasites are seen. In some capsules only transverse sections of the parasite can be seen, while in others longitudinal, and in still others the whole parasite can be observed arranged in a spiral or coiled condition. As many as eight parasites can be seen in one field with a two-thirds inch objective and one inch eye-piece (Bausch and Lomb).

The capsules contain, besides the parasites, a certain quantity

of granular material most evident at each end, a few small, oval, apparently vacuolated cells and an occasional small round cell.

Around the capsule is seen in many areas a marked round-celled accumulation, with some few spindle-shaped cells; other capsules show this change to only a slight degree.

A few capsules are devoid of parasites; the walls of such capsules are intensely thickened, and some contain vacuolated cells and granular detritus; the latter may be calcareous matter.

Mast cells are abundantly scattered throughout the specimen.

Sometimes three and four parasites are found within one capsule; in the sections studied in the case here reported but one parasite could be identified in any capsule.

The following blood counts were made:

*April 3, 1901.* Hemoglobin, 48 per cent.; erythrocytes, 4,336,000; leukocytes, 12,680. Differential count of leukocytes: Finely granular oxyphiles, 65.5 per cent.; coarsely granular oxyphiles (eosinophiles), 4 per cent.; lymphocytes, 21 per cent.; hyalin, 9 per cent.; basophiles, 0.5 per cent.

*April 11th.* Hemoglobin, 80 per cent.; erythrocytes, 4,275,000; leukocytes, 17,600. Differential count of leukocytes: Finely granular oxyphiles, 63 per cent.; coarsely granular oxyphiles (eosinophiles), 2.5 per cent.; lymphocytes, 27.5 per cent.; hyalin, 7 per cent.

*April 21st.* Hemoglobin, 72 per cent.; erythrocytes, 5,200,000; leukocytes, 20,000. Differential count of leukocytes: Finely granular oxyphiles, 68.5 per cent.; coarsely granular oxyphiles (eosinophiles), 3 per cent.; lymphocytes, 22.5 per cent.; hyalin, 6 per cent.

*May 4th.* Hemoglobin, 71 per cent.; erythrocytes, 5,212,000; leukocytes, 21,500. Differential count of leukocytes: Finely granular oxyphiles, 69 per cent.; coarsely granular oxyphiles (eosinophiles), 3.5 per cent.; lymphocytes, 22.5 per cent.; hyalin, 6 per cent.

The granules of the finely granular oxyphiles were generally markedly oxyphilic, but could not be taken for eosinophiles.

*Remarks on Trichinosis.* Tiedemann in 1822 and Hilton in 1832 noticed calcified cysts in the muscle, and Leidy in 1847 first found the parasite in the hog.

In 1845 Owens discovered the *trichina spiralis* in a cadaver in the dissecting-room. In 1848 the same parasite was found by Herbst.

It is well known that Zenker,<sup>1</sup> in 1860, was the first to call attention to the disease trichinosis, and almost at the same time Leuckhart confirmed the relationship of the parasites as a cause of the disease. In 1862 Friedreich<sup>2</sup> first diagnosticated the affection and experimentally determined the presence of the parasites in the living subject.

In experiments upon birds the trichinæ advanced in development in the intestine, but failed to invade the muscular system.

Embryo trichinæ are generally present in the intercostal muscles, muscles of the eye, larynx, and tongue, but can be found in almost any muscle of the body. In the case just reported the most severe infection seems to be localized in the gastrocnemius muscle, although sections of the deltoid also show the presence of the parasites. In the limbs they are more abundant in the muscles nearest the trunk.

Not only do the trichinæ encyst themselves in the voluntary muscles, but also in the panniculus adiposus and in the coats of the intestine. In the larger muscles the parasites are most numerous near their tendinous end. The heart rarely contains trichinæ. The parasite possesses great powers of resistance to putrefaction, being found alive one hundred days after exposure; they survive three days' exposure to temperatures of 22° to 25° C. According to Perroncito,<sup>3</sup> the parasite resists a temperature of 48° to 50° C. for only a few minutes; other observers, however, claim that a temperature of 60°, 70°, or 80° C. is necessary to kill.

According to Roberts,<sup>4</sup> the muscle fibers involved are generally, upon microscopic examination, found to be more or less destroyed and the interstitial connective tissue increased.

Dr. Sutton,<sup>5</sup> harpooning a small mass of gastrocnemius muscle in a fatal case of trichinosis, found it swarming with trichinæ, "estimated at more than one hundred thousand to the square inch;" the parasites were in active motion, "coiling and uncoiling."

Tyson<sup>6</sup> mentions that the capsule may undergo fatty degeneration, which takes place at times early, but may be delayed for years. The worm-cyst lies usually with the long axis parallel to the muscle fibers.

A. M. Lewin<sup>7</sup> points out that the trichinal myositis has its seat entirely in the muscle elements, whereas anthrax myositis is confined to the connective tissue. In Dr. Da Costa's case the increase in connective tissue seems to be between as well as in the muscle fibers.

R. Langerhans claims that trichinae, together with their capsules, are subject to degenerative changes and eventually reach a stage of elimination from their host. He further claims that recovery is never complete until the total elimination of both parasite and capsule takes place.

The oval cells seen within the capsules are, according to Heller,<sup>8</sup> "oval, vesicular-shaped muscle nuclei," formed by the thickened sarcolemma.

The edema of the parts involved is said by Colberg<sup>9</sup> to be due to the obliteration of the capillaries of the muscles in which the trichinae become embedded. Klob<sup>10</sup> suggests that the edema may be produced by the lymphatic channels becoming plugged with the parasites, and the lymph-stream thus obstructed. Hamilton<sup>11</sup> thinks that the edema is of an inflammatory nature, due to the irritation caused by the parasites.

According to Sterling and Verco,<sup>12</sup> the capsule of the cyst is chitinous and lamellated, varying a good deal in thickness according to the part of the cyst examined and to its age, being always thickest at the poles and in the oldest cysts, least dense and most transparent in young cysts and about the equator. They also mention that as many as six or seven trichinae may be found in a common capsule.

Pagenstecher, Chatin, Cerfontaine, and Askanazy<sup>14</sup> state that the female trichinae penetrate into the intestinal villi and deposit their embryos in the lymph vessels, whence their migration occurs.

*Remarks on Eosinophilia.* The blood-counts here recorded do not show an unusual increase in the percentage of eosinophiles.

Brown<sup>13</sup> claims that there is constantly a relative increase in the eosinophiles, which may reach 68 per cent.

Eosinophilia is by no means pathognomonic of trichinosis, as the same condition is noticed in other processes.

Turk, in pneumonia, found a post-critical eosinophilia of 5.67 per cent.; after acute articular rheumatism, 9.37 per cent. Even

after the injection of tuberculin eosinophilia may be noticed, and Zappert in several cases records 26.9 per cent. of eosinophiles.

Osler,<sup>15</sup> in five cases of trichinosis (diagnosis is confirmed by finding the parasites in the muscles), found quite a pronounced eosinophilia in each case. In the first case T. R. Brown (the clinical clerk) gives 37 per cent. eosinophiles. Up to the date of the patient's discharge the eosinophiles averaged 16.8 per cent. The second case, counted by Dr. Fitcher, showed 44 per cent. eosinophiles. The third case, counted by Dr. Gwyn, showed 45 per cent. eosinophiles. The fourth case, counted by Dr. Thayer, showed 48 per cent. eosinophiles. The fifth case, counted by Dr. Gwyn, showed from 22 to 36 per cent. eosinophiles; and after the "patient had been up and about for three weeks" the eosinophiles were more than 60 per cent.

Sears,<sup>16</sup> reporting a case of trichinosis, found in the first count 17.5 per cent. and in a second count 13 per cent. of eosinophiles. A well-marked urticarial eruption was present over the trunk and thighs.

In Lambert's and Brook's case of trichinosis, quoted by Ewing,<sup>17</sup> there was no evidence of transformation of neutrophils into eosinophiles, although some of the eosinophile granules were unusually small.

Blumer reports a case in which there was 50 per cent. eosinophiles; a recovering case by Brook gave 83 per cent. Ewing claims that from 40 to 60 per cent. are usually found, but in some periods they may fall to 8 or 10 per cent. The eosinophilia is usually persistent, 15 per cent. remaining after four and one half months in a case reported by Stump, and 34 per cent. after five months in a case reported by Brown.

R. J. Patek<sup>18</sup> reports a case in which there were 30 per cent. eosinophiles—the trichina spiralis being found in a sample of sausage from which the case had its origin.

In infections by other animal parasites, as the ankylostoma duodenale, Müller and Rieder found 8.2 to 9.7 per cent. Zappert also noticed eosinophilia in the same condition.

Bucklers<sup>19</sup> found 16 per cent. eosinophiles in a case of oxyuris vermicularis; 19 per cent. in ascarides. Lichtenstein found 3.4 per cent. in a case of tenia mediocanellata and 72 per cent. in a

case of ankylostomiasis. He also reports 13.5 per cent. of eosinophiles in a case of *anguillula stercoralis*.

Grawitz regards the increase of eosinophiles in afebrile stages of malaria as of diagnostic import. Zappert, in a case of malaria one day after the last attack, found 20.34 per cent. eosinophiles.

Engel, in varicella, when the pustules were healed, found 16 per cent. eosinophiles. Six per cent. of eosinophiles has been observed by Wickery in von Jaksch's anemia infantum.

Ehrlich claims that there is a marked eosinophilia in leukemia, and further states that this is a pathognomonic sign of the disease.

Reinbach found an increase in the number of eosinophiles in the blood of patients suffering from malignant neoplasms. In a case of sarcoma of the forearm, one of the thigh, and one of the abdomen the percentage of eosinophiles ranged from 7 to 10 per cent.

Neusser considers eosinophilia as one of the diagnostic signs of sarcoma of the bone-marrow, and he found an eosinophilia in osteomalacia.

In one case of lymphosarcoma of the neck, with metastasis in the bone-marrow, he found 60,000 eosinophiles per cubic millimeter.

Exclusion of the splenic function may also be followed by eosinophilia. After the internal administration of camphor in two cases of chlorosis van Noorden noticed an increase of eosinophiles up to 9 per cent. In bronchial asthma Gollasch has found from 10 to 20 per cent. eosinophiles. In skin diseases (prurigo and psoriasis) Canon noticed in a large number of cases 17 per cent. eosinophiles. In a marked case of urticaria Lazarus found 60 per cent. eosinophiles.

Laptschinsky<sup>20</sup> mentions the presence of a very large number of coarsely granular leukocytes (eosinophiles?) in a case of relapsing fever.

Gabritschensky found 11 to 22 per cent. eosinophiles in emphysema, while Fisk reports 14.6 per cent. and Billings 53.6 per cent., the latter out of 8300 cells. Fuchs and Teichmüller found many eosinophile cells in various forms of bronchitis.

Zappert found 8 to 19 per cent. of eosinophiles in four cases of uncomplicated chorea. Cabot also refers to twelve cases showing eosinophilia, and in myxedema the same observer found 5 and 4 per cent. respectively in two cases.

Hock and Schlesinger found 20 per cent. in one subject suffering with rhachitis, and Weiss 16 per cent. in the same disease.

Loos claims that in syphilis the eosinophile cells are increased, especially when the eruption is extensive.

Klein has recently reported a case of hemorrhagic septicemia in which the eosinophiles reached 76 per cent. in the pleural exudate and 40 per cent. in the blood. Aporti found as high as 18 per cent. eosinophiles in the intermittent pyrexia at the end of the disease.

Turk found 5 per cent. eosinophiles in the second week in a case of measles.

Ewing cites that the eosinophiles reach a maximum of from 8 to 15 per cent. in the second or third week in scarlet fever, decline slowly, and reach normal at about the sixth week.

To Professor Coplin I wish to extend my sincere thanks for the interest he has shown in the case and for the photomicrographs presented.

I also wish to extend my thanks to Drs. Butler and Dorsett, resident physicians of St. Joseph's Hospital, for their interest manifested in the case and assistance in perfecting the blood-count.

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## DISCUSSION.

DR. COPLIN said that at the meeting of the Boston Association of American Pathologists he suggested the possibility of a recrudescence of lesions. The evidence upon which to base such a view is by no means conclusive, but may be briefly summed up as follows:

1. A more or less local, active lesion (trichina, edema, myositis, etc.), with trichina present in other muscles which at the time manifest no symptoms.

2. The absence of marked eosinophilia so commonly observed in the initial outbreak of trichiniasis.

3. The history of injury and the well-known fact that injury induces inflammation of fully encapsulated, but quiescent, parasites of other but similar types—*e. g.*, *echinococci*.

4. The evident pericapsular lymphoid accumulation, which is apparently most evident around the older capsules, thereby establishing to my mind that such active inflammatory phenomena as are present at this time are not of necessity related to the presence of living trichinæ.

The assumption that different broods of parasites are disseminated from a single mother may seem at first to negative the suggested view that recrudescence is possible, but it does not appear to me as conclusively inconsistent with the idea expressed. It seems quite difficult to understand exactly how one brood should infiltrate one extremity to the exclusion of other muscles.

*June 27, 1901.*



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